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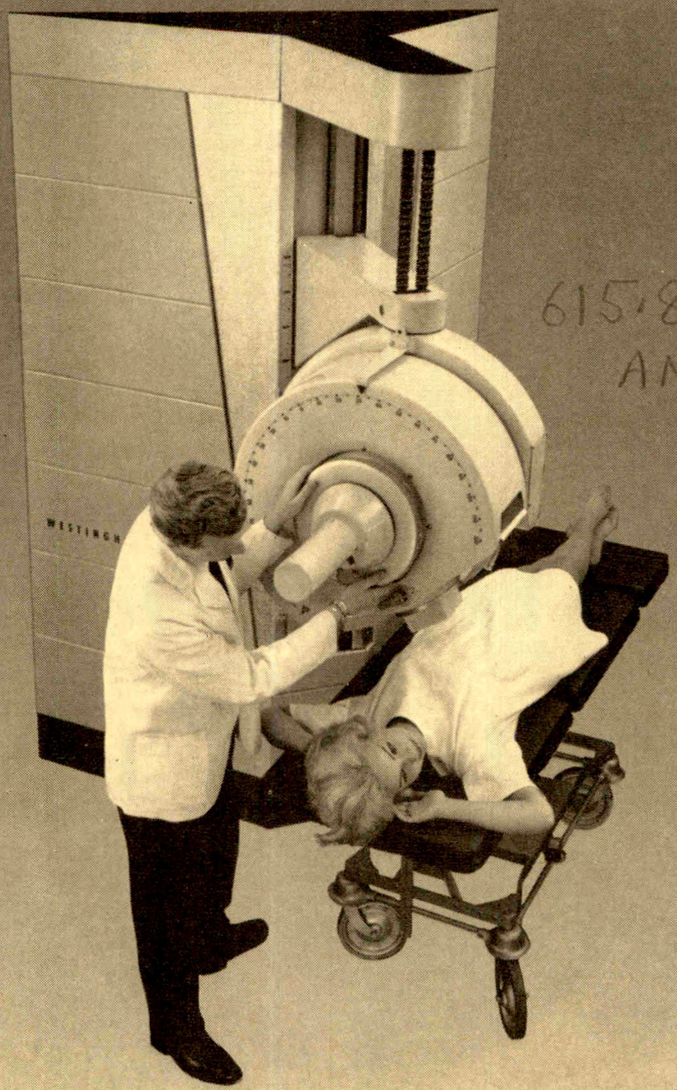

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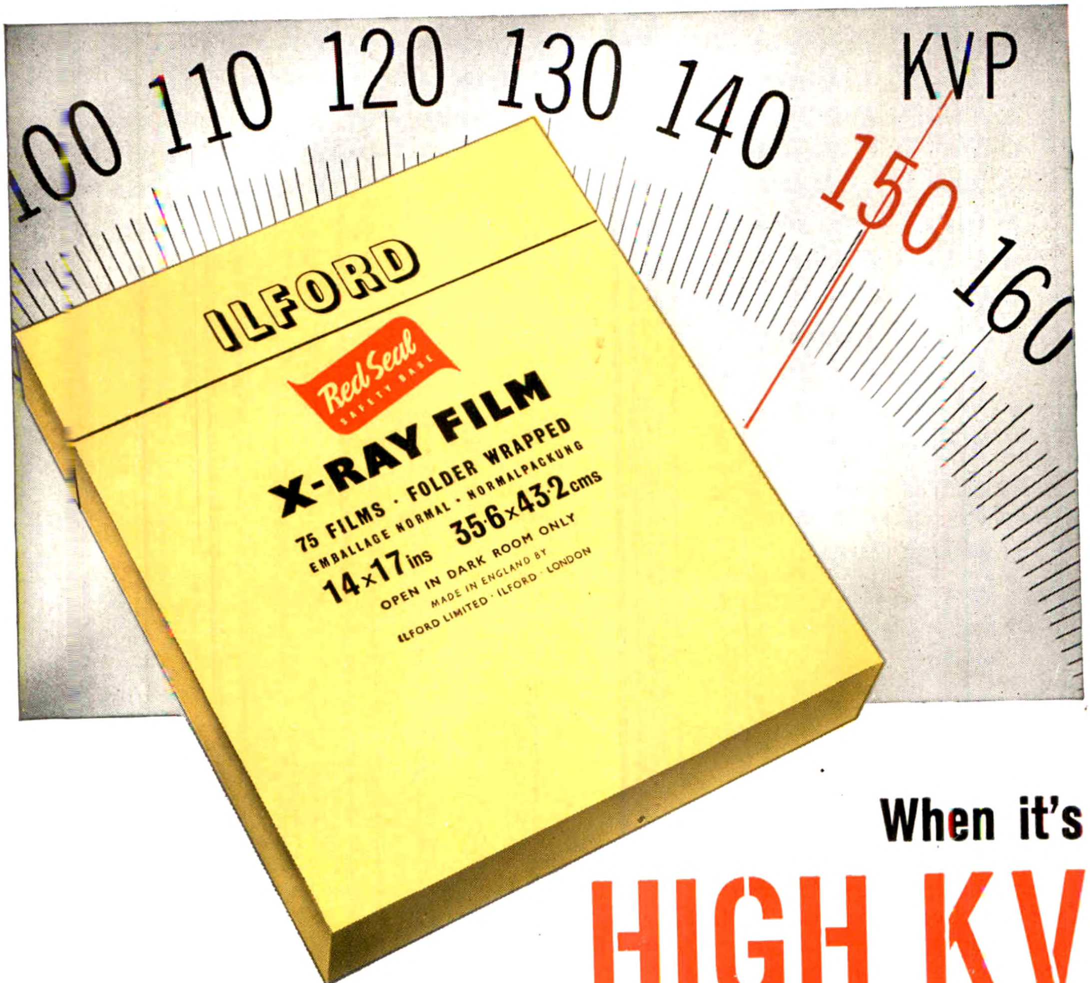

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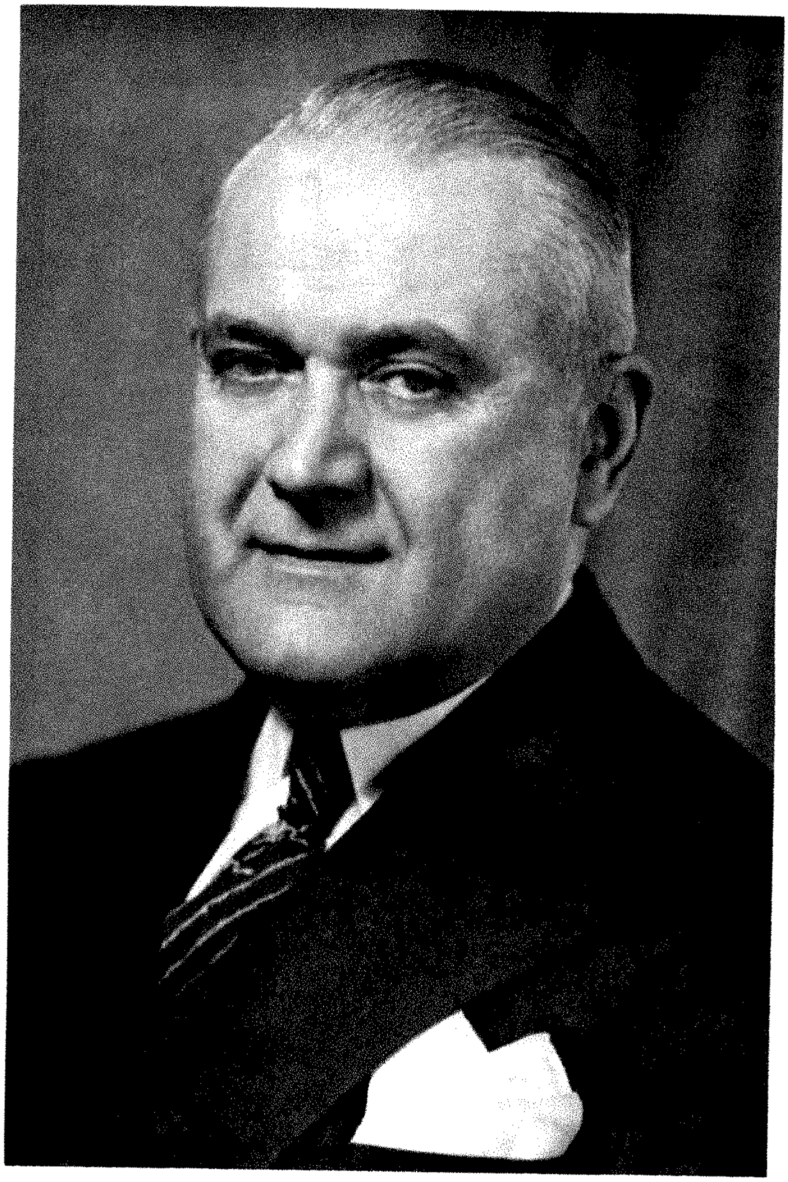


TRAIAN LEUCUTIA
Caldwell Lecturer

THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 85 JANUARY, 1961 No. 1

HEURISTIC GLIMPSES INTO THE EVOLUTION OF RADIATION THERAPY*

PARTICULARLY IN REFERENCE TO GYNECOLOGIC CANCERS CALDWELL LECTURE, 1960

By TRAIAN LEUCUTIA, M.D.
DETROIT, MICH.

At the threshold of the fifth decade of a brilliant series of annual lectures given in memory of Doctor Eugene Caldwell, it is with a sense of deep humility and understandable timidity that I rise to give the fortieth lecture.

Dr. Caldwell died a martyr in 1918, at the time when the precisely regulated incandescence of the tungsten cathode of a therapeutic roentgen ray tube became a reality. Although his contributions were greatest to diagnostic radiology, he also devised in 1902 a treatment tube for insertion into body cavities and continued to maintain a keen interest in the development and improvement of other types of tubes applicable to therapeutic radiology. As an electrical engineer and physicist at the beginning and as a physician later, he was a technical perfectionist, a great creative genius, and above all an inspirational idealist. In severe self-criticism he said of himself:[25] "One must necessarily make statements which are more or less dogmatic and in which the 'personal equation' is an important factor." Personal equations are attributes of true pioneers who in their never flagging zeal leave indelible impressions upon their successors. The American Roentgen Ray Society has a long list of dauntless pioneers, many of whom became martyrs. The name of Eugene Caldwell, in a way, has become a symbol of their zeal, perseverance and faith.

I am profoundly grateful to Dr. Reineke for the honor of having been chosen to give this fortieth lecture. I am also indebted to Dr. Reineke for accepting my topic of this evening, for, in view of the rapidly expanding interest in radiation therapy, this affords me the opportunity for some heuristic glimpses into its evolution, from the era of the "cranky" apple-green gas tubes to the present era of modern equipment and precision technology.

"HEURISTIC," serving to find out, has become an expression for a method of investigation that aids in the discovery or interpretation of facts and truths ever since the Greek philosopher, Archimedes, exclaimed, "Eureka!" in his elation at discovering the now universally known Archimedean principle. The comparatively young science of radiology and more particularly the science of radiation therapy has, as no other branch of medicine, encountered formidable difficulties in its slow rhythmic evolution. The necessity

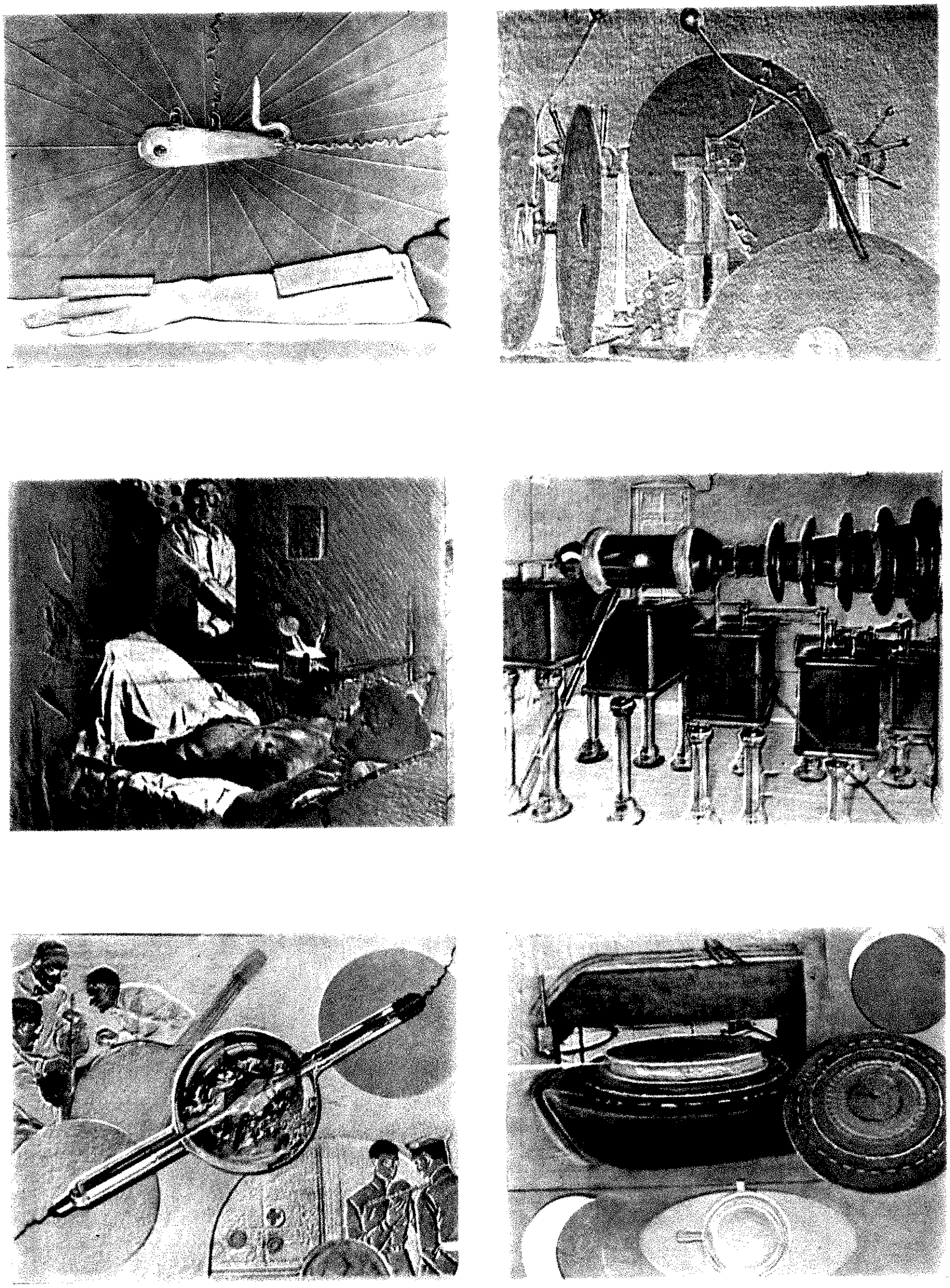
* Presented at the Sixty-first Annual Meeting of the American Roentgen Ray Society, Atlantic City, New Jersey, September 27–30, 1960.

of relying on rays, whether they be vibratory or particulate, which cannot be seen by the naked eye, the extremely complex ways by which these rays are produced, measured physically and assayed in their biologic action, and the determination of their true place among other, considerably older, treatment methods constituted problems which could be approached only in the light of contemporary technical and medical achievements. Some of these problems have been successfully solved, others—still too perplexing—continue to form a tempting challenge to the inquiring mind. Such a problem is a study of the salient phases influencing most profoundly the development of radiation therapy and thereby establishing its usefulness in the treatment of the large group of gynecologic cancers. Heuristic glimpses into the discoveries of the time may help in properly interpreting the facts resulting from these discoveries.

As was to be expected, in the beginning, soon after the discovery in 1895 by Röntgen of the "invisible ray" which was to illuminate the medical world, treatment with this new kind of ray was acclaimed with enthusiasm. The memorable discoveries which Finsen made with ultraviolet rays at the turn of the century had a marked effect also on radiation therapy especially in the dermatologic field, where it was first applied. Since it was necessary that the Finsen ultraviolet rays produce, for therapeutic effect, "a reaction which may vary in degree from an erythema to a vesicular or bullous dermatitis," it was assumed that a similar reaction ought to be produced by roentgen rays. The importance of this reaction, which was variously called "x-ray inflammation" or "x-ray burn," was emphasized by practically all the radiotherapists at that time. To quote Rinehart:[26,27] "The method employed was to cover the healthy skin with thin sheet lead, and to expose the sore or part to be treated for five minutes at 8 inches the first day, increasing the time of exposure and shortening the distance each day until a decided inflammatory reaction was obtained, a low vacuum tube giving a soft green light being used. I have been unable to obtain any benefit in any case of the kind without an inflammatory reaction." The voltage range which usually was expressed in spark-gap distance was low, varying from 50 to 100 kv. Because of the lack of penetration of the roentgen rays and the fact that they were used for treatment of lesions lying on the surface or near the surface of the skin, the term "superficial roentgen therapy" was later coined for this form of treatment. By 1904, it had found such widespread use that Professor Brocq of the Hôpital Broca of Paris, in a preface to J. Belot's treatise on *Radiotherapy*, wrote: "Radiology was born but yesterday; it has already made enormous strides. To-day it may be said to dominate the therapeutics of dermatology."

Although the risk of a "deep burn in hope of quickly destroying the tumour" was justifiable in the treatment of skin cancer and other malignant neoplasms, the production of "x-ray inflammation" for the treatment of many benign conditions, together with the vagaries of the machines used, led to some unexpected and often disastrous results. Thus, the period of great enthusiasm was followed by a period of even greater pessimism. To quote Mac Kee:[22] "The failure to substantiate the early therapeutic results, the injurious effects observed as time went on, and the fact that there was no satisfactory method of estimating or of controlling the quantity and quality of radiation administered resulted in a period of depression or pessimism which endured from about 1906 to about 1912." A perusal of the literature during this period is replete with recitals of cases of "severe x-ray burns" and "a few deaths" and A. R. Robinson[28] in the October 6, 1906 issue of the *British Medical Journal* made the statement: "The roentgen rays have been far too widely employed, almost justifying their designation as race suicide machines."

In 1910, Kassabian[17] wrote: "With the employment of the roentgen rays for thera-



Composite bas-relief mural tableaux based on contemporary photographs, sketches and etchings (Harper Hospital).

peutic purposes, burns have now become a common accident. In several instances suits were brought against physicians on the ground that they did not use the necessary means of protection; in most of these cases the severe character of the diseases demanded so severe a treatment that burning had to be contended with." Dr. Kassabian in the very same year became himself a martyr to roentgen injuries due to this lack of protection. His list of physicians who were sued contained some of the prominent names of the time both from this country and Europe.

During this most discouraging phase in the evolution of radiation therapy, Dr. Hickey,[12] Founder and first Editor of this Journal, journeyed to New York to personally witness a preliminary demonstration given Saturday evening, December 27, 1913, at the Hotel St. Denis of a new form of roentgen tube, invented by Dr. Coolidge[6] of Schenectady, honorary member of this Society. In an inspired editorial, Dr. Hickey immediately announced this epoch-making event to the world with the statement: "This contribution to roentgenology is, in the words of Prof. Shearer of Cornell University, the most important which American genius has ever offered." At the time of demonstration, the therapeutic value of the tube was wholly untried, but Dr. Hickey conjectured that "owing to the extreme exhaustion, penetrating rays of the therapeutic value of the gamma rays of radium may be produced. This, of course, opens up the most wonderful new possibilities for treatment."

The progress that followed was swift. The development of a suitable high voltage energizing source for operation of the new tube, continuous improvements in design of its electron emissivity, the introduction of autotransformer control of the primary voltage and proper rectification of the secondary voltage paved the way, as clinical therapy moved forward in great strides.[7,8] Superficial roentgen therapy (50–130 kv.) at once emerged from its era of pessimism, and since 1914, to again quote Mac Kee[22] has "stood the test of time," thus inaugurating a period of "realism;" medium roentgen therapy (130–170 kv.) was laid on a sounder foundation.

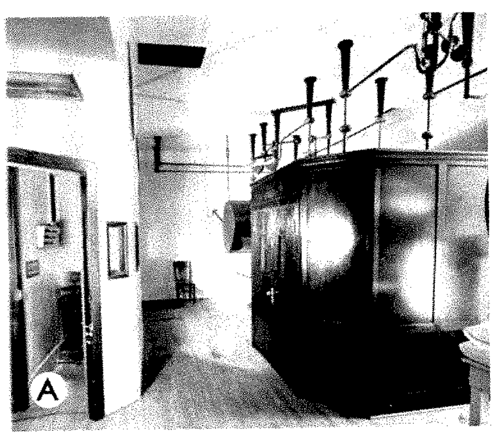
This swift progress provided the American Expeditionary Forces in World War I with the best equipment up to that time[18] and it was the good fortune of my distinguished mentor of this evening, young Captain Lawrence Reynolds, to be the recipient at the American Ambulance Hospital No. 1, later called the American Military Hospital No. 1, of the first Coolidge tube overseas. This tube was presented for inspection to General Pershing himself on his visit to the hospital.

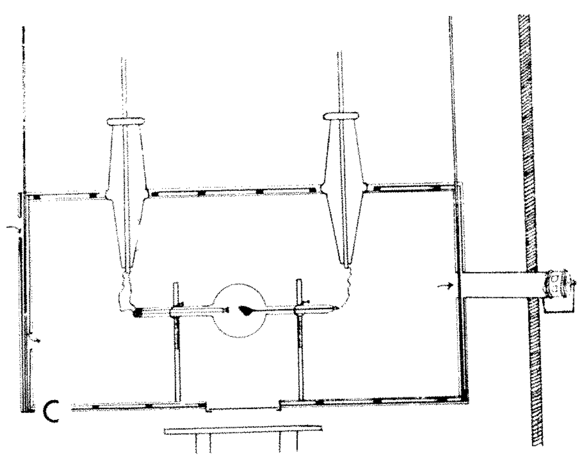
It may be said that the introduction of the Coolidge tube has revolutionized therapeutic radiology. Its range was rapidly extended to 200 kv., establishing in the early 1920's the solid basis of deep roentgen therapy or, as we now prefer to call it following the suggestion of Dr. Garland, orthovoltage roentgen therapy. This form of treatment gave such impetus to the clinical application of radiation that during the subsequent decade, which was to become so fertile scientifically, most notable contributions were made not only to technical development but also to our knowledge of the action of radiation on normal and pathologic tissues. The more penetrating roentgen rays could now reach any depth of the body, thus enabling careful biologic, physiopathologic and histopathologic observations. These contributions were further enhanced by similar observations made with the even more penetrating gamma rays of radium, which during this decade also began to find gradually increasing clinical applicability.

The first orthovoltage roentgen therapy unit at Harper Hospital was installed in 1921. Since, to cite Dr. James Case,[5] "We have not yet reached the stage of providing proper protection against the higher voltage tubes," a fact which earlier had led to such disastrous results with the lower voltage tubes, the preliminary efforts were directed to construction of devices for pro-

tection from both electrical and radiation hazards. Another disturbing element was the very low output of the original air-cooled tubes necessitating very long treatment times. Mr. Clifford Sherratt, electrical engineer and pioneer designer of high voltage radiation protection, honorary member of this Society, aided immeasurably in solving these contemporary problems so that at the beginning of 1922 routine clinical therapy was made possible.

The first unit had two air-cooled tubes which were housed in suspended self-contained lead drums and energized by a single transformer, enabling treatment of two patients simultaneously (Fig. 1, *A*, *B* and *C*). In the second unit the two tubes were housed in lead boxes and used for the treatment of the same patient through two opposite ports simultaneously; one box was placed beneath the treatment table and the other was suspended above it, with a flexible up and down movable arrangement (Fig. 2, *A* and *B*). For the third unit, a water-cooled tube with a much higher output which had become available was utilized and from this time on only one tube was energized by each transformer. The original lead drum was bisected and its upper half was replaced by a lead cubicle, which contained first the water-cooling and later the oil-cooling device of the tube (Fig. 3). One single patient was treated by each unit, the tube being fixed and the treatment table being moved up and down for the desired skin target distance. Orthovoltage units of this type were employed very successfully until recently when they were replaced by flexible shock-proof and radiation-proof apparatus provided with the del Regato mirror localizer and an aperture with a platform arrange-





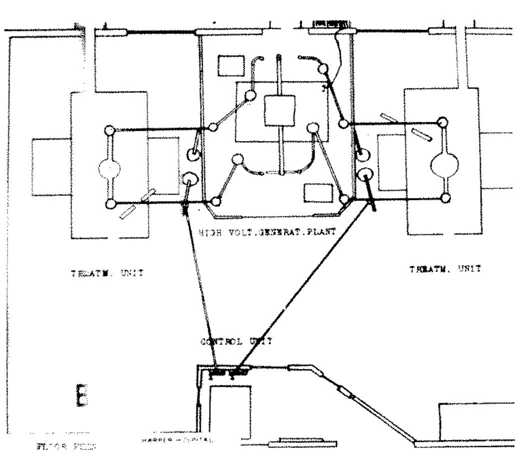


FIG. 1. First orthovoltage unit installed at Harper Hospital in 1921. (*A*) Photograph of the treatment room. A single transformer energized two air-cooled tubes which were housed in suspended self contained lead drums, enabling treatment of 2 patients simultaneously. (*B*) Floor plan showing the lay out of the unit. (*C*) Diagram of the lead drum.

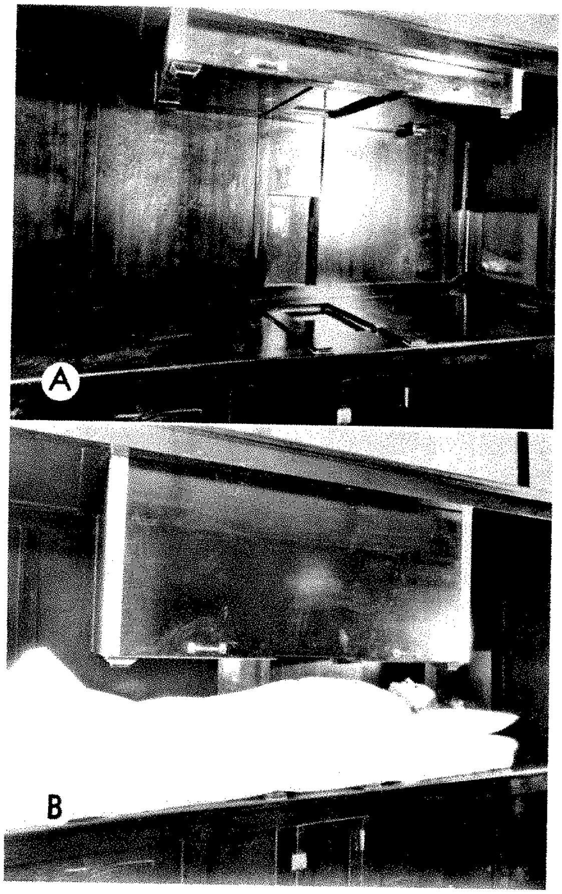


Fig. 2. Second orthovoltage unit. (*A* and *B*) The two air-cooled tubes were housed in individual lead boxes, one box being placed beneath the treatment table and the other suspended above it with a flexible up and down movable arrangement. This unit permitted treatment of a patient through two opposing ports simultaneously.

ment for geometric or anatomic outlining of the treatment fields.

As a result of promising experimental work by a few investigators at the threshold of the 1930's, a supervoltage roentgen therapy unit was added in 1931 and patients were treated by it starting in 1932. Briefly, the unit consisted of six 150 kv. constant potential cascaded transformers (Fig. 4) and a Lauritsen type unisectional tube with grounded anode.[21] This unit also underwent several modifications. Initially, two interchangeable heads were used, one of steel with a thin tungsten disk target and another of brass with a some-

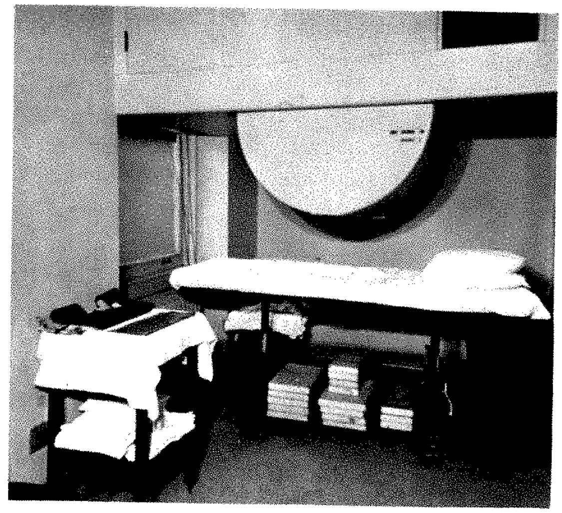


Fig. 3. Third orthovoltage unit. When a water-cooled tube with a much higher output became available, the lead drums of Figure 1 were bisected and their upper halves were replaced by lead cubicles which contained the water-cooling and later the oil-cooling system. The treatment table was moved up and down for the desired skin target distance, wooden blocks of various thicknesses being used for this purpose.

what thicker gold disk target. During this period only one patient was treated at a time. Then a change was made to a "transparent" lead target (Fig. 5, *A*, *B* and *C*), the filament current was improved, and the controlling rod was insulated more firmly (Fig. 6). Since the transparent target was at a 45° angle, this permitted, with

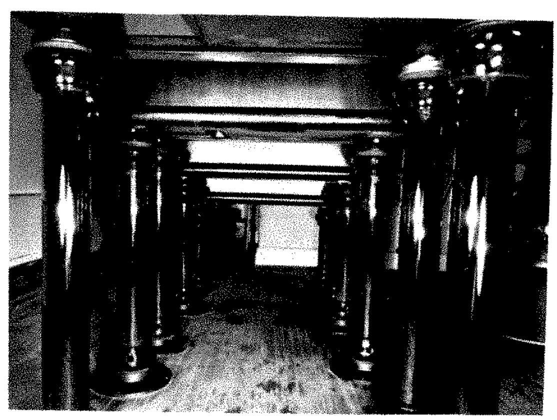


Fig. 4. First supervoltage unit installed at Harper Hospital in 1931. The energizing source consisted of six 150 kv. constant potential cascaded transformers.

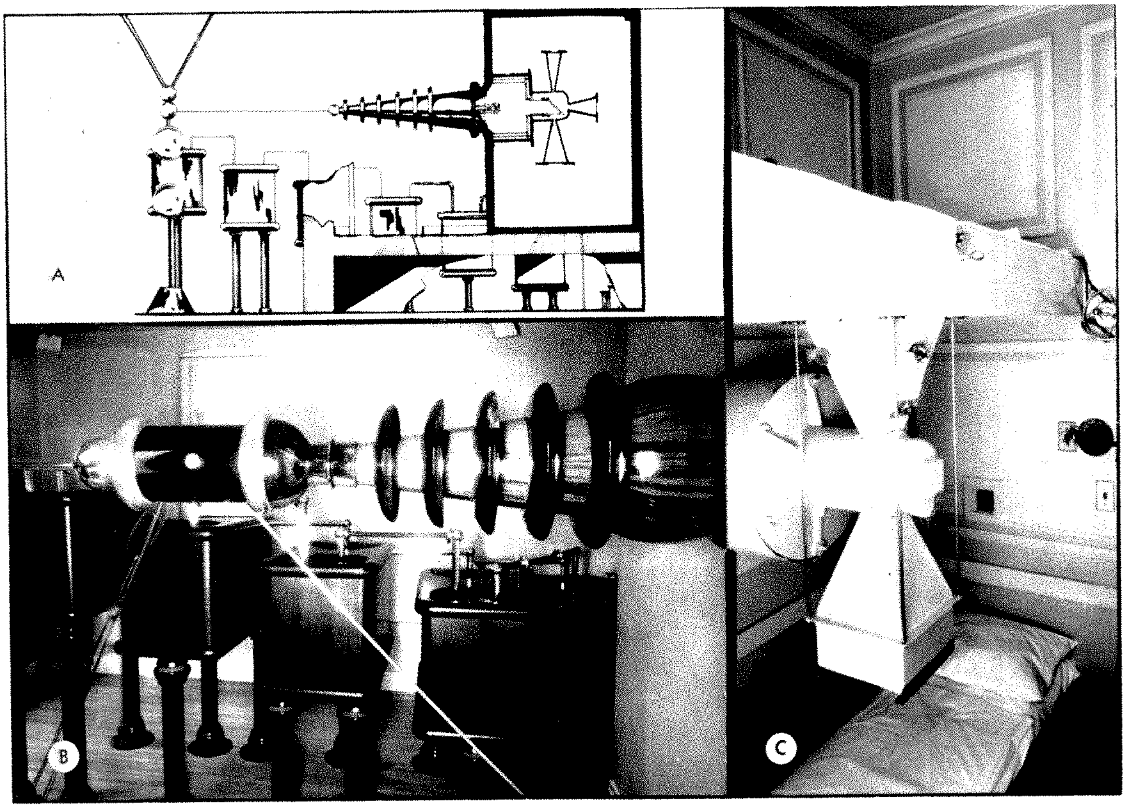


Fig. 5. Later improvement of the supervoltage unit. (*A*) Diagram of the unit. (*B*) Room of the generating plant containing the six constant potential cascaded transformers and the porcelain body of the Lauritsen type unisectional tube. (*C*) Lead-protected treatment room with a periscope window for observation and a loud speaker for communication. The transparent lead target of the anode grounded tube permitted treatment of 2 patients simultaneously. A third (axial) portal could be used at the same time for investigative purposes.

a slight filter correction, an equal output for two opposite fields. Thus 2 patients could be treated simultaneously, one in an upper berth with a fixed skin target distance and the other on a lower mobile table with a more flexible arrangement. Provision was also made for a third (axial) field which could be used at the same time for investigative purposes.

This unit was operated at 500–600 kv. constant potential, with 7 mm. Cu equivalent filtration, corresponding to a half value layer of 9 mm. Cu. The output was 20 r/min. at 50 cm. and the skin target distance of the mobile table could be varied between 50 and 70 cm. The protection which was designed by Mr. Sherratt was foolproof and the patients were observed during treatment by a built-in periscope. The unit was employed successfully for a quarter of a century. It was replaced four years ago by a 2 mev. Van de Graaff apparatus and the periscope for observing the patients was substituted by a closed circuit television system.

Of course, there are other types of apparatus, such as the betatron, the synchrotron, and the linear accelerator, and some teletherapy units with radioactive sources as Co^{60} and more recently Cs^{137} which notably augment the spheres of radiation therapy, but their consideration transcends the scope of our discussion this evening.

With the equipment available at Harper Hospital, an impressive number of diseases has been treated since the first orthovoltage unit was installed. The gyne-

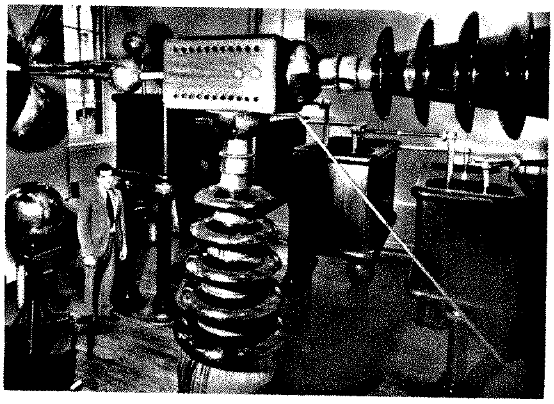


Fig. 6. Still later improvement of the supervoltage unit showing porcelain insulation of the filament supply generator.

cologic cancers represent a group in which radiation therapy, more than in any other group, was used extensively from the beginning. The series upon which this study is based includes 3,204 cases treated from 1922 to 1954, of which 592 cases were malignant neoplasms of the ovary, 2,059 cases were carcinoma of the cervix uteri and 553 cases were carcinoma of the endometrium. For a comparable evaluation of the results obtained with the various radiation modalities or their combinations with surgical methods, the five year survival rate is taken as the measuring yardstick and patients who could not be followed-up were assumed to have died from cancer. From 1922 to 1931 roentgen therapy was carried out with orthovoltage rays, from 1932 to 1936 half of the patients were treated by orthovoltage and the other half by supervoltage rays and since 1937 supervoltage rays have been used exclusively in all patients. An important change was also made as regards the general policy for radium application. Prior to 1928 the practice was to administer a dose which would produce little or no reaction on the surrounding normal structures, particularly those of the intestinal and urinary tracts. After 1928, the factitional reactions were considered to be unavoidable, and the radium dose was considerably increased. Commensurate with this, the orthovoltage roentgen dose was also increased and, finally, the full substitution of the supervoltage for the orthovoltage rays since 1937 led to a rather standardized and fairly uniform technique.

In malignant neoplasms of the ovary, the majority of which were carcinomas, the generally accepted method of combining surgery with external roentgen therapy was used throughout the series. Often alternation of surgery, consisting of removal of the primary neoplasm or of the larger recurrent or metastatic masses, and roentgen therapy was employed, particularly in tumors of lesser radiosensitivity.

The treatment of malignant neoplasms of the ovary is fraught with two great difficulties. First, the average case, because of absence or paucity of symptoms in the beginning, is diagnosed at a relatively late stage of disease after the dissemination has already taken place; secondly, the nature of the dissemination itself in the form of peritoneal implants or metastases to the regional lymph nodes is such that it entails special considerations in outlining the irradiation procedure. As is well known, the regional sphere of the ovary, even before the malignant neoplasm has broken through the ovarian capsule and produced peritoneal implants, is in the para-aortic area. The lymph channels originating in the ovary follow the course of the ovarian artery and lead to the upper lymph nodes of the para-aortic group. This means that in the majority of cases radiation therapy, to be effective, must include the upper abdomen in addition to the pelvis and lower abdomen. Since some irradiation of the kidneys cannot be avoided, the possible late effect produced on this organ must be weighed against the biologic longevity of the malignant neoplasm, which is a serious limiting factor. The presence of ascites, which accompanies dissemination both to the peritoneum and the high para-aortic lymph nodes in a high percentage of cases, is another serious limiting factor.

The problem of what program to follow is hard to solve. We generally made use of a plan according to which the more radio-

sensitive neoplasms received the largest doses possible in a relatively short time, whereas tumors of the adult type were irradiated with several less intensive fractionated courses over longer periods and were alternated with surgery. In not a few cases a prolongation of life beyond the five year period was obtained after as many as 3 to 4 operations followed by even more courses of radiation therapy.

The five year survivals in the 592 cases, arranged quinquennially, are given in Table 1. As may be seen, some improvement was obtained throughout the years, the over-all results rising from 18 to 31 per cent. However, the contribution of supervoltage radiation therapy which was used routinely after 1937 was rather disappointing. This series does not as yet reflect the effect of the use of instillation of various radioactive substances or chemical agents into the peritoneal cavity but it already appears that the over-all five year results will be little influenced with this new addition and that combined surgery and external radiation therapy will continue to remain the most acceptable method of treatment.

Table I

MALIGNANT NEOPLASMS OF OVARY
FIVE YEAR SURVIVALS
1922–1954

Period	Cases/Survivals	Per Cent
1922–26	39/7	18
1927–31	60/11	18
1932–36	85/14	16
1937–41	82/20	24
1942–46	91/23	25
1947–51	128/34	27
1952–54	107/33	31

Total Cases Treated: 592.

Unlike the malignant neoplasms of the ovary, carcinoma of the cervix uteri was the subject of most intense and controversial discussions for nearly half a century in respect to the type, extent and radicalism of the many procedures periodically recommended for its treatment. Of these, the various irradiation methods occupied a place no less conspicuous than the multitude of surgical techniques, and the appraisal of their relative merits became a difficult task. A review of a large series of cases with a heuristic glimpse into the salient chronologic phases of the evolution of treatment may aid in elucidating some aspects of the complex problem.

While caustic agents and various forms of cauterizations have been used for the treatment of carcinoma of the cervix uteri from time immemorial, its complete eradication has been attempted only since the development of surgery. The zenith of the surgical phase was reached during the second decade of the present century with the very radical Wertheim operation. It soon was realized, however, that, because of the great operative mortality, the high incidence of postoperative sequelae and the disappointing over-all five year survival results, a different approach to the problem was desirable. In 1915 radium therapy made its appearance and in the early 1920's it was complemented by orthovoltage roentgen therapy utilizing 200 kv. After another decade, and especially following the introduction of supervoltage roentgen therapy, irradiation with a combination of radium and roentgen rays became the predominant method, completely replacing surgery. At the height of this radiation phase, Dr. Kamperman,[15] Chief of the Department of Obstetrics and Gynecology at Harper Hospital, wrote in 1941, "There is now sufficient collected evidence to warrant the statement that the greatest of advances in the treatment of cervical carcinoma was made when the gynecologist relinquished the surgical treatment for radiation therapy."

Within a few years, however, notable contributions from Taussig,[30] Meigs,[23,24] Brunschwig[3,4] and others were published with the purpose of reviving and expanding the radical surgical procedures used either alone or in combination with various forms and sequences of radiation therapy. This aim stemmed mainly from three facts: first, in a certain number of cases radiation

therapy failed to bring about the desired results; secondly, the reactions which followed particularly the irradiation of the more resistant types of lesions were considered to be too severe; and thirdly, and most important of all, the tremendous development in the surgical techniques made possible the use of very extensive, commando type operations with complete safety to the patient. Although great emphasis was placed on the institutional investigative nature of these formidable procedures and the necessity of specially equipped teams to carry them out, the impact on the generally accepted treatment methods of the time could not be avoided, thus inaugurating the reintroduction of the surgical phase in the treatment of carcinoma of the cervix uteri.

The series of 2,059 cases of carcinoma of the cervix uteri treated at Harper Hospital from 1922 to 1954 by various methods reflects with fairly realistic fidelity the trends of the times. Of these, 1,958 were cases of carcinomas originating in the cervix of an intact uterus, and 101 were cases of primary carcinomas of the cervical stump in which a hysterectomy had been performed years previously for a benign condition. Radiation therapy, with intracavitary radium and external roentgen rays, was employed most frequently but a significant number of cases also had surgical procedures in various combinations. In the entire series the following four methods were used: (A) preoperative irradiation with external roentgen rays and intracavitary radium, followed within six to eight weeks by surgery and possible further irradiation; (B) radical surgery, followed by two to three courses, at eight to ten weeks from each other, of external roentgen therapy, complemented occasionally by intravaginal radium; (C) irradiation alone, consisting whenever possible of two courses of external roentgen therapy and intracavitary radium, at an interval of eight to ten weeks; and (D) irradiation alone in cases of recurrence after radical surgery.

The over-all five year survivals for the series, arranged quinquennially, are given in Table II which shows a continuous improvement in the results obtained. For the eight year period from 1947 to 1954, the over-all five year survival rate was practically 50 per cent.

For the purpose of studying the impact of the three aforementioned chronologic phases in the evolution of treatment, the 1,958 cases of carcinoma of the cervix uteri proper were arranged in five sexennial and one triennial period as follows: I. 1922–1927; II. 1928–1933; III. 1934–1939; IV. 1940–1945; V. 1946–1951; and VI. 1952–1954. The 101 cases of primary carcinoma of the cervical stump, which were treated by irradiation alone, will be considered separately.

As may be noted from Table III some patients already had been treated by a combination of preoperative irradiation and surgery (method A) during Period I; then the method was completely abandoned. It was revived during Periods V and VI. The five year survival rates ranged from 50 per cent during Period I to 70 per cent during Period VI, the average for Periods V and VI being 60 per cent. Only Stage I and II carcinomas were subjected to this type of combination, accounting for the increased survivals. Due, however, to the fact that they represented a small fraction of the total group, they had only a slight influence on the over-all results. A similar observation was made recently by Frick

TABLE II

CARCINOMA OF CERVIX UTERI
FIVE YEAR SURVIVALS
1922–1954

Period	Cases/Survivals	Per Cent
1922–26	236/36	15
1927–31	196/38	20
1932–36	267/81	30
1937–41	288/106	31
1942–46	420/187	40
1947–51	435/212	49
1952–54	217/115	50

Total Cases Treated: 2,059.

et al.[1] who state that "The application of radical surgical methods of treatment to primary surgical cancer has been associated with slight, but statistically not significant, improvement in the total cure rate." Rutledge and Fletcher,[29] who studied the effect of combination of megavoltage (22 mev.) irradiation and radical lymphadenectomy in Stage III carcinomas of the cervix, likewise express the opinion that "more intensive series and longer follow-up time will be necessary to determine whether there are changes in the salvage rate." Furthermore, there is already some evidence accumulating that, because of the usual postoperative sequelae which cannot be avoided and the marked increase in radiation fibrosis associated not infrequently with formation of lymphoceles, such combined treatment constitutes a radical procedure apt to be followed by an increased number of late complications. For these reasons one may affirm that, until full evaluation is obtained, the reintroduction of radical surgery following irradiation will continue to remain purely an investigative method.

The number of cases treated in our series by radical surgery and postoperative irradiation (method B) was practically the same throughout the six periods (Table III). As a rule, only the early cases were subjected

Table III

CARCINOMA OF CERVIX UTERI
FIVE YEAR SURVIVALS WITH COMBINED METHOD
1922–1954

Period	A Cases/Survivals	Per Cent	B Cases/Survivals	Per Cent
I. 1922–27	10/5	50	22/8	36
II. 1928–33	0/0	0	17/11	60
III. 1934–39	0/0	0	21/10	50
IV. 1940–45	2/1	50	33/16	50
V. 1946–51	25/14	56	26/13	50
VI. 1952–54	10/7	70	14/8	58
Total Cases	47/27	57	133/66	50

A. Preoperative irradiation, surgery.
B. Surgery, postoperative irradiation.

Table IV

CARCINOMA OF CERVIX UTERI
FIVE YEAR SURVIVALS WITH IRRADIATION IN RECURRENCES AFTER RADICAL SURGERY
1922–1954

Period	D Cases/Survivals	Per Cent
I. 1922–27	38/2	5
II. 1928–33	9/0	0
III. 1934–39	8/0	0
IV. 1940–45	4/0	0
V. 1946–51	9/2	22
VI. 1952–54	2/0	0
Total Cases	70/4	6

D. Surgery, recurrence, irradiation.

to this combination of treatment. The five year survival rate, excepting Period I, was 50 per cent or over. This contrasts sharply to the results obtained in recurrent cancers (method D) when the radiation therapy following radical surgery was prescribed only after the recurrent or metastatic lesions became manifest. As may be seen in Table IV, the largest number of such patients was treated during Period I when the surgical phase was still dominant. The results obtained were disastrous and continued to remain so during all subsequent periods in the greatly reduced number of cases in which it was used, the five year survival rate barely reaching 6 per cent.

In compiling the results obtained by irradiation alone (method C), the relative results were tabulated in addition to the absolute results for comparison (Table V). The former group includes all patients who received at least two full courses of irradiation eight to ten weeks apart, as has been the standard procedure in our institution since 1937. The latter group also comprises a certain number of patients who, for various reasons, received only one full course of irradiation, others in whom even one course could not be completed and all those patients who were treated for distant dissemination of the disease. Table V shows that, while the relative results obtained with the two course technique, excepting

Table V

CARCINOMA OF CERVIX UTERI
FIVE YEAR SURVIVALS WITH
IRRADIATION ALONE

Period	Absolute		Relative	
	Cases/ Survivals	Per Cent	Cases/ Survivals	Per Cent
I. 1922–27	197/26	12	—	—
II. 1928–33	214/46	21	—	—
III. 1934–39	304/99	33	103/45	44
IV. 1940–45	412/175	42	315/157	50
V. 1946–51	413/195	47	340/171	50
VI. 1951–54	168/85	51	131/71	54

Total Cases Treated: 1,708.
The relative group includes only cases which had 2 full (or several partial) courses of irradiation, eight to ten weeks apart.

the first few years, remained practically the same, the absolute results rose steadily and during Period VI approximated the relative results. This table also shows that comparatively more patients were treated to the full extent from period to period, thus indicating a more favorable stage of the disease at the initiation of the irradiation.

Analysis of the ratios of the cases treated by the three combined methods (A, B, and D) to each other and to the cases treated by irradiation alone (C) permits the following deductions (Table VI):

Table VI

CARCINOMA OF CERVIX UTERI
RATIO OF COMBINED METHOD CASES TO
IRRADIATION CASES
1922–1954

Period	Ratio A B C D
I. 1922–27	5.0:10.1:100:19.3
II. 1928–33	0.0: 7.9:100: 4.2
III. 1934–39	0.0: 6.9:100: 2.6
IV. 1940–45	0.5: 8.0:100: 1.0
V. 1946–51	6.1: 6.3:100: 2.2
VI. 1952–54	5.8: 8.2:100: 1.2

A. Preoperative irradiation, surgery.
B. Surgery, postoperative irradiation.
C. Irradiation alone.
D. Surgery, recurrence, irradiation.

(1) Preoperative irradiation followed by radical surgery (method A), which was used to some extent initially, has been replaced by irradiation alone (method C); the combination was reintroduced in the mid-1940's but its scope is being restricted to more and more rigidly selected cases. The sexennial ratio to the cases treated by irradiation alone was 5.0:100 in Period I, then it dropped to 0 and rose to 6.1:100 in Period V and 5.8:100 in Period VI.

(2) Radical surgery followed by postoperative irradiation (method B) continued to be used in approximately the same proportion, particularly in the early cases. The sexennial ratios ranged from 6.3:100 in Period V to 10.1:100 in Period I.

(3) Irradiation of recurrent carcinomas following radical surgery (method D) persistently yielded extremely poor results and therefore is now used very rarely. The high sexennial ratio of 19.3:100 in Period I gradually dropped to a low of 1.2:100 in Period VI.

It may, therefore, be stated that in the treatment of carcinomas of the cervix uteri irradiation constitutes the major method. The optimal results are obtained by a comprehensive combination of intracavitary radium or other radioactive substances and external irradiation with roentgen or gamma rays. As reflected in this extensive series, all improvements in the over-all five year results throughout the years have been contributed chiefly by some important advance in technologic development or by a more judicious selection of the modalities used for irradiation. The effect of reintroduction of radical surgery upon the over-all results appears to be statistically small and needs further investigative evaluation.

In studying the 101 cases of primary carcinomas of the cervical stump in which a hysterectomy was performed years previously for some benign condition, two interesting observations were made. (1) The introduction of an intravaginal radium technique protracted over seven days, as a complement to the external supervoltage roentgen therapy, more than doubled the

survival results obtained. As shown in Table VII, whereas during the first three sexennial periods the five year survivals averaged 22 per cent, since 1940 they have risen to between 54 and 59 per cent for the three subsequent periods. (2) However, even more interesting and greatly surprising is the fact that, as shown in Table VIII, the ratio of incidence of primary carcinoma of the cervical stump to that of carcinoma of the cervix of an intact uterus rose from 2.6:100 during Period I to 12.3:100 during Period VI, or more than a five-fold increase. The patients in this group were referred for radiation therapy, which was used as the sole method, on an average thirteen years after hysterectomy, the range extending from one year to fifty years. The increase in the ratio started after World War II and was marked during Periods V and VI. Apart from perhaps an effect of changing population in an industrial area, no explanation is available for this phenomenon. As far as could be determined not one of these patients had previous radiation therapy in any form for the benign condition for which the hysterectomy was performed.

The heuristic approach assumes even a greater significance in the appraisal of the optimal method of treatment in carcinoma of the endometrium, encompassing the lesions of the corpus and fundus uteri. The medical literature contains numerous notable publications dealing with the use of various techniques of radiation therapy and their possible combinations with surgical procedures to achieve the highest statistical yield in the results obtained. In some of these publications preoperative irradiation, either in the form of intracavitary radium application alone or in association with external radiation therapy, is recommended; in others irradiation, usually in the form of external radiation therapy, is prescribed postoperatively; and still in others surgery alone is used and irradiation is reserved for those instances in which recurrence or dissemination has occurred. There is general agreement on the fact that irradiation, as the sole method of treatment, should be undertaken only in the inoperable cases, mostly for the purpose of palliation.

Table VII

CARCINOMA OF CERVICAL STUMP
FIVE YEAR SURVIVALS WITH IRRADIATION
1922–1954

Period	Cases/ Survivals	Per Cent
I. 1922–27	7/0	0
II. 1928–33	4/1	25
III. 1934–39	7/3	29
IV. 1940–45	17/10	59
V. 1946–51	43/23	54
VI. 1952–54	23/13	56
Total Cases Treated:	101	

Table VIII

RATIO OF CARCINOMA OF CERVICAL STUMP TO
CARCINOMA OF CERVIX
1922–1954

Period	Cervical Stump Cases	Cervix Cases	Ratio
I. 1922–27	7	267	2.6:100
II. 1928–33	4	240	1.6:100
III. 1934–39	7	333	2.1:100
IV. 1940–45	17	451	3.8:100
V. 1946–51	43	473	9.1:100
VI. 1952–54	23	194	12.3:100
Total Cases:	101	1,958	

In our series of 553 cases of carcinoma of the endometrium treated from 1924 to 1954 by radiation therapy and surgery in various combinations, three methods were used: (A) preoperative irradiation with intracavitary radium and external roentgen rays, hysterectomy six to eight weeks later, and postoperative irradiation with external roentgen rays two to three weeks after the operation; (B) hysterectomy and 2 or 3 courses of postoperative irradiation with external roentgen rays, associated very rarely with intravaginal radium, at intervals of eight to ten weeks from each

other; and (C) irradiation alone in the inoperable cases.

The physical factors of the irradiation, as in carcinoma of the cervix, conformed to the technical improvements of the time. Until 1924, when radiation therapy of carcinoma of the endometrium was started at Harper Hospital, surgery constituted the sole method of treatment. Radium was used occasionally on a trial and error basis, mostly in the inoperable and recurrent cases. The favorable impression gained in conjunction with carcinoma of the cervix, where deep roentgen therapy was started two years earlier, soon led to a fundamental change in this situation. First, the inoperable cases of carcinoma of the endometrium were subjected to combined radium and roentgen therapy, then the operable cases, in which hysterectomy was performed, were irradiated postoperatively with roentgen rays. Initially, here too as in carcinoma of the cervix, the dosage with both agents was rather low so as to avoid any distressing side reaction. After a few years, however, the fallacy of such a policy became evident and the dosage was raised considerably.

In 1928, Dr. Kamperman[15,16] conceived the plan of preoperative irradiation in carcinoma of the endometrium, consisting of a full course of intracavitary radium and external roentgen therapy. By placing radium within the uterine cavity, it is possible to achieve a more thorough irradiation of the entire pelvis than is the case with postoperative roentgen therapy alone, after the uterus has been removed. There are two other reasons why such a procedure appears more advantageous. First, it provides a technique for performance of dilatation and curettage and insertion of intrauterine radium at the same time. If the microscopic examination of the curettings indicates the presence of a functional or polypoid endometrium, the radium dose is adjusted to produce exovulation, without supplemental roentgen therapy. However, if the report is that of a carcinoma, the radium application is prolonged and is followed by a full course of roentgen therapy which, then, constitutes the preliminary irradiation. Experience over the years shows that, since carcinoma of the endometrium is for the most part a postmenopausal occurrence with fresh, often dramatic, hemorrhage as its most common symptom, such a procedure leads to a somewhat earlier diagnosis in the average case. Secondly, as confirmed by the experiments of Altemeier and Jones,[1] the preliminary irradiation of the pelvis reduces the hazards of infection, almost completely eliminating operative mortality.

The preliminary irradiation is followed within six to eight weeks, depending on the reaction produced, by surgery. The operative procedures varied to some extent in our series, but in the majority of cases a total hysterectomy with bilateral oophorectomy, as recommended by Kamperman, was performed.

A second course of irradiation, consisting of roentgen therapy alone, is administered within two to three weeks after the hysterectomy.

This method has been used in Harper Hospital cases continuously since its introduction in 1928. The only modifications were made in 1933 when, for four years, half of the cases were treated with supervoltage roentgen therapy for comparison, and in 1937 when orthovoltage roentgen therapy was completely replaced by supervoltage roentgen therapy.

During the same time a significant number of patients, who had had hysterectomy first and in whom roentgen therapy was advised postoperatively, was accepted for irradiation from other institutions. The majority of these patients received the maximum allowable radiation dose but, excepting a few instances, without the benefit of intracavitary radium. This circumstance permits a good comparison of the two methods.

In the inoperable cases irradiation alone was used, consisting of two courses of external roentgen therapy and intracavitary radium at an interval of eight to ten weeks, whenever possible.

The over-all five year survivals arranged

Table IX

CARCINOMA OF ENDOMETRIUM
FIVE YEAR SURVIVALS
1924–1954

Period	Cases/Survivals	Per Cent
1924–26	12/4	33
1927–31	29/13	45
1932–36	49/25	47
1937–41	83/46	55
1942–46	92/58	63
1947–51	189/113	60
1952–54	99/63	64
Total Cases Treated:	553	

quinquennially are shown in Table IX. As may be noted, there was a steady and definite improvement in the results. Since 1937, when the present procedures had become fairly well standardized, the quinquennial survival rates have increased from 55 to 64 per cent. Despite the fall to 60 per cent during the period of 1947 to 1951, this represents a notable progress which, as we shall see, may be explained by studying the change in combination of the methods used.

Based on the aforementioned historic evolution, the series of 553 cases of carcinoma of the endometrium may be divided into those treated before and those treated after 1937. However, to gain a better insight into the constancy of the results, the latter cases are again divided into those of the first ten years after 1937 and those of the next eight years. Thus we may distinguish three periods: I. 1924–1936; II. 1937–1946; and III. 1947–1954. As may be seen from Table X the five year survival rates of the patients treated according to method A amounted to 80 per cent during Period I and II and to 78 per cent during Period III. The corresponding rates for the patients treated with method B were 50 per cent for Period I and II and 55 per cent for Period III. The cases treated by irradiation alone (method C) yielded a five year survival rate of 35 per cent during Period I, 40 per cent during Period II and 35 per cent during Period III. The over-all results for all cases were 47 per cent during Period I, 60 per cent during Period II and 61 per cent during Period III.

Three deductions may be made from a comparative analysis of these results.

1. The marked superiority of method A over method B has continued to be evident throughout the three periods.

2. This continued superiority of method A has altered the aspect of the entire series in two ways: (a) it has increased the ratio of the operable cases to the inoperable cases from 11:10 during Period I to 14:10 during Period II and 30:10 during Period III (Table XI), representing a three-fold increase. However, even more significant is the

Table X

CARCINOMA OF ENDOMETRIUM
FIVE YEAR SURVIVALS RELATED TO METHOD OF TREATMENT
1924–1954

Period	A		B		A and B Cases Combined		C		A, B and C Cases Combined	
	Cases/Survivals	Per Cent	Cases/Survivals	Per Cent	Cases/Survivals	Per Cent	Cases/Survivals	Per Cent	Cases/Survivals	Per Cent
I. 1924–36*	10/8	80	37/19	50	47/27	58	43/15	35	90/42	47
II. 1937–46	64/52	80	39/19	50	103/71	70	72/33	40	175/104	60
III. 1947–54	143/101	78	73/40	55	216/151	70	72/25	35	288/176	61

Total Cases Treated: 553.
A. Preoperative irradiation, hysterectomy, postoperative irradiation.
B. Hysterectomy, postoperative irradiation.
C. Irradiation alone in inoperable cases.
* Method A was started in 1928.

Table XI

CARCINOMA OF ENDOMETRIUM
RATIO OF OPERABLE CASES TO
INOPERABLE CASES
1924–1954

Period	Operable Cases A and B	Inoperable Cases C	Ratio
I. 1924–36*	47	43	11:10
II. 1937–46	103	72	14:10
III. 1947–54	216	72	30:10

* Method A was started in 1928.

fact that (b) within the operable group itself it has raised the ratio of preirradiated operable cases (method A) to the postirradiated operable cases (method B) from 3:10 during Period I to 16:10 during Period II and 20:10 during Period III (Table XII), or nearly a seven-fold increase.

3. The increase in the number of the cases operated upon was accompanied by a corresponding decrease in the number of cases which remained to be treated by irradiation alone. Thus the ratio of the preirradiated inoperable cases (method A) to the inoperable cases (method C) was 2:10 during Period I, 9:10 during Period II and 20:10 during Period III (Table XIII). In the two periods after 1937 when both method A and method C had become fairly well standardized the decrease was slightly

Table XII

CARCINOMA OF ENDOMETRIUM
RATIO OF PREIRRADIATED OPERABLE CASES TO
POSTIRRADIATED OPERABLE CASES
1924–1954

Period	Preirradiated Operable Cases A	Postirradiated Operable Cases B	Ratio
I. 1924–36*	10	37	3:10
II. 1937–46	64	39	16:10
III. 1947–54	143	73	20:10

* Method A was started in 1928.

Table XIII

CARCINOMA OF ENDOMETRIUM
RATIO OF PREIRRADIATED OPERABLE CASES TO
INOPERABLE CASES
1924–1954

Period	Preirradiated Operable Cases A	Inoperable Cases C	Ratio
I. 1924–36*	10	43	2:10
II. 1937–46	64	72	9:10
III. 1947–54	143	72	20:10

* Method A was started in 1928.

over two-fold. In other words, more than twice as many patients were subjected to method A treatment during Period III than during Period II. This had two effects on the over-all results of the series during these periods: (a) it reduced the survival rate for method A from 80 per cent during Period II to 78 per cent during Period III and (b) it also reduced the survival rate for method C from 40 per cent during Period II to 35 per cent during Period III. Due to the fact that the favorable effect of preliminary irradiation helped to extend the criteria of operability, more of the questionable borderline cases have been transferred to group A, leaving only the more severe cases in group C. Although this less rigid selection of cases produced slight lowering of the five year survival rates for both groups individually, the two-fold increase in the ratio of cases subjected to method A, with its superior results during Period III, has raised the over-all results to 61 per cent as compared to 60 per cent during Period II.

It may, therefore, be stated that in the treatment of carcinoma of the endometrium a combination of surgery and irradiation plays a major role. The optimal results are obtained by a method consisting of preoperative irradiation with intracavitary radium or equivalent radioactive substances and external roentgen or gamma rays,

followed within six to eight weeks by total hysterectomy and bilateral oophorectomy, and supplemented, when necessary, with a second course of external radiation therapy. Irradiation alone is used only in the cases adjudged inoperable primarily or following completion of the preliminary irradiation when surgery still remains contraindicated.

Of course, in viewing the problem of treatment of gynecologic cancers in a broader perspective, there are other factors of greater importance which must be considered. Among these are the natural history of the cancer, its histopathologic structure, the mode of its local and metastatic spread, and, foremost, its biologic behavior with respect to anatomic site, whether located in a silent area as malignant neoplasms of the ovary, in an area of insidious onset as cancer of the cervix or in a dramatically symptomatic area as cancer of the endometrium. The over-all five year survivals of 31 per cent, 50 per cent, and 61 per cent in the three respective areas amply reflect this inescapable conclusion. The immense contribution of radiation therapy in helping to bring about these results, however, cannot be denied. Thus, the almost insurmountable task of the early pioneers, of whom so many became heroic martyrs, in establishing the clinical merit of radiation therapy has been "wonderfully" fulfilled.

My great teacher, Preston M. Hickey,[13] who in his Caldwell Lecture of 1928 artfully epitomized the life history of Eugene Caldwell and who skillfully reviewed all his important contributions to radiology, concluded his lecture by saying: "The speaker's task will not have been in vain if you who make up this assembly are strengthened and encouraged by the glimpses which we have had of one who so nobly exemplified the ideals of our specialty." It is my ardent hope that you who make up this distinguished assembly this evening are equally strengthened and encouraged by the "heuristic" glimpses which we have had of the slow rhythmic evolution of radiation therapy, particularly in reference to the treatment of gynecologic cancers. To paraphrase the words of the ancient philosopher, "To know the truth is not as important as to love the truth."

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DEMONSTRATION OF LYMPH NODE METASTASES BY PELVIC VENOGRAPHY*

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PROGNOSIS in carcinoma of the cervix is in great part dependent upon the presence or absence of pelvic lymph node involvement.[1] While radioresistance of the neoplasm may be a possibility, certainly it has not been uncommon in patients dying of cancer of the cervix to find the treated primary lesion under control but considerable residual disease in the pelvis. In a collected series of cases[7] treated by surgery, a 61 per cent five year survival was reported when the pelvic lymph nodes were normal as compared to a 21 per cent five year survival if these nodes were involved by metastatic cancer. The incidence of positive pelvic lymph nodes as reported by Graham and Graham[6] is 15 per cent for LON† I, 27 per cent for LON II, and 66 per cent for LON III. This high incidence makes control of the lymphatic dispersions a critical problem in the treatment of cancer of the cervix.

There can be no doubt that irradiation can destroy tumor in the pelvic lymph nodes, although the frequency with which this occurs and the necessary dosage range is not known.[3,14,16] Kottmeier[10] has presented patients with positive pelvic lymph nodes who, on re-exploration years after radiation therapy, failed to show evidence of tumor. In a series[15] of patients staged as LON III who were treated with the betatron to a minimum of 6,000 r whole pelvis irradiation with subsequent lymphadenectomy, the incidence of histologically positive lymph nodes was well below the expected incidence of unirradiated cases.

Because of the inability to predetermine involvement of the lymph nodes, present techniques of radiation therapy include the usual lymph node sites within the treatment field. This needlessly results in extensive and potentially hazardous irradiation for those many patients whose lymph nodes are not involved. If the presence of these metastatic lymph nodes were known, more vigorous treatment would be justified and the cases without lymph node involvement could be spared this irradiation safely.

Lymph node involvement has been shown to be equally significant in cases of persistent disease. In a series of patients where exenteration was performed for persistent cancer, Bricker and Butcher[4] found only 2 out of 19 patients with positive lymph nodes who survived for three years. This is contrasted to a survival of 25 out of 56 patients when the lymph nodes were negative. Furthermore, the recognition of involved para-aortic lymph nodes would eliminate needless laparotomies, since such involvement makes these patients incurable.

The main groups of lymph nodes affected by metastatic carcinoma from the cervix lie along the vascular channels of the pelvis.[14] The venous channels, being thin-walled and of low intraluminal pressure, are easily distorted by enlarged and firm lymph nodes. This finding has been confirmed by several authors.[2,7]

TECHNIQUE

The veins of the pelvis can be opacified by several methods. The injection of a contrast medium into the marrow of the pelvic bones and the trochanteric region of the femur has been used.[7,11] The findings by this method are somewhat indirect and the opacification of the veins probably is less optimal than by a more direct route. This method is also subject to a low but definite incidence of pulmonary emboli, osteomyelitis and other complications.[12] Injection of

† LON = League of Nations staging.

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the contrast medium into the dorsal vein of the clitoris[7] and interstitial injection into the uterus also have been used to opacify the pelvic veins. We have selected the direct approach advocated by several authors.[2,6,8,9]

The technique is quite simple. It consists of bilateral percutaneous puncture of the femoral veins and passage of polyethylene catheters into the external iliac veins over metal guide wires. The tip of the catheter lies approximately 10 cm. distal to the junction of the internal and external iliac veins. Twenty-five cc. of 25 per cent hypaque is injected simultaneously into both catheters as quickly as possible and roentgenograms are obtained using a rapid film changing device.

The examination is carried out in two stages: the first without compression of the inferior vena cava, and the second with compression by a plastic balloon.

Roentgenography is done with the patient in the supine position, although occasionally additional oblique projections are utilized. With this technique, excellent opacification of the major vessels is obtained. The veins are fully distended by the large bolus of the medium and the opacification is nearly optimal with this direct approach. At the completion of the examination, excretory pyelograms are made sparing the patient an additional injection of contrast medium.

We have had no significant complications in our series of 31 cases. Helander and Lindbom[8] reported only 1 case with a serious complication. This consisted of pulmonary infarcts and emboli following a thrombus in the femoral and iliac veins. Early in our study, the tip of the guide wire broke off in the soft tissues in 2 patients. This was due to faulty manufacture of the wire and, since correction of this defect, no further complications have occurred.

NORMAL FINDINGS

Without compression of the inferior vena cava (Fig. 1), the external and common iliac veins and the inferior vena cava, as well as any abnormal filling of the venous channels, are well seen. With compression (Fig. 2), there is retrograde filling of the internal iliac vein down to the level of a competent valve. While somewhat variable, this distance is approximately 5 cm. from the junction of the internal and external iliac veins. Usually the obturator vein does not fill.

Several normal variations may occur within the veins of the pelvis. These have been pointed out by Helander and Lindbom[8] and by Bartley,[2] who have studied these veins both in operative cases and in the postmortem status when they are in a fixed, expanded state. While usually there is a single internal iliac vein on both sides, at times there may be two vessels (internal and middle iliac) on one or both sides of the pelvis. Occasionally, an internal iliac vein enters the common iliac vein in the region of the promontory. Normally, the iliac artery and aorta, as they cross the left common iliac vein, may indent and compress it. Indentations may also appear at the junction of the external and internal iliac veins due either to compression by the internal iliac artery or to "jet" dilution if no reflux occurs. While reflux into the internal iliac veins usually occurs down to a symmetric level, occasionally the competent valve is located higher on one side than the other. Reflux into the internal iliac veins may occur without compression, although in Bartley's[2] experience this was either bilateral or not at all. Filling of one or both ascending lumbar veins occurs without compression.

PATHOLOGIC FINDINGS

The presence of a firm tumor mass adjacent to the thin-walled, low-pressure vein may make itself apparent in several ways:

(1) *Indentation of the vein* (Fig. 3, 4, 5 and 7). This must be differentiated from the normal indentations. Abnormal indentations usually occur about the junction of the internal and external iliac veins and along the posterior and lateral margins of the common iliac veins, where normal indentations do not occur.

(2) *Nonfilling of a part of the vein because*

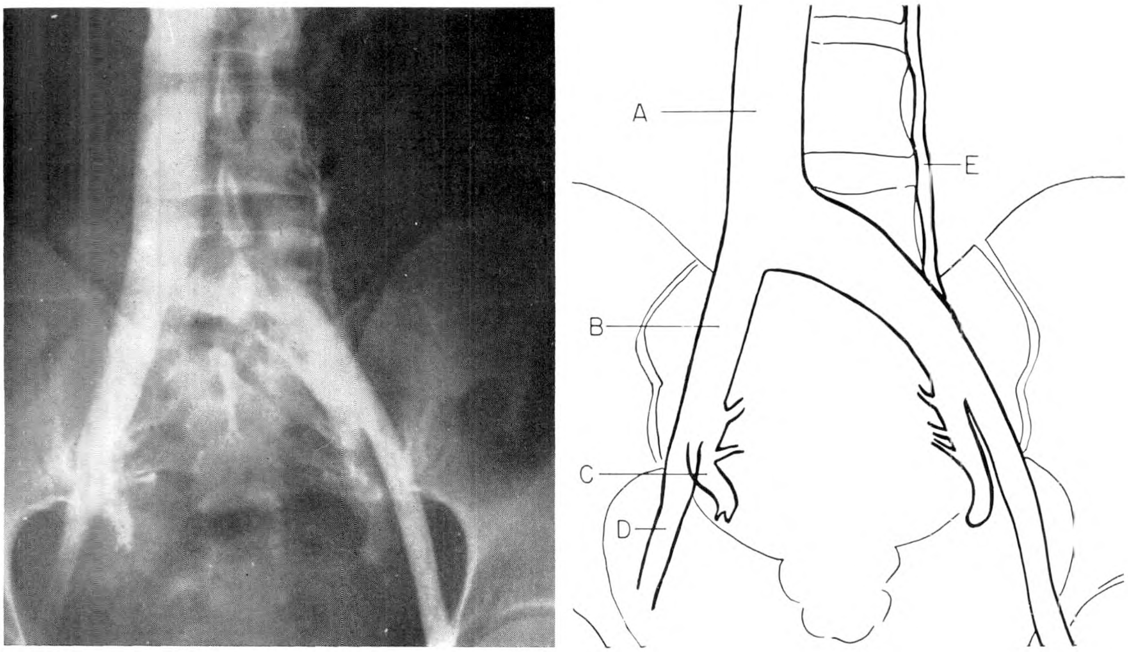


FIG. 1.

Normal pelvic venogram without compression. On the diagram, *A*—inferior vena cava, *B*—right common iliac vein, *C*—hypogastric vein, *D*—external iliac vein, *E*—ascending lumbar veins. Reflux into the internal iliac veins can occur normally without compression, as can filling of either or both ascending lumbar veins.

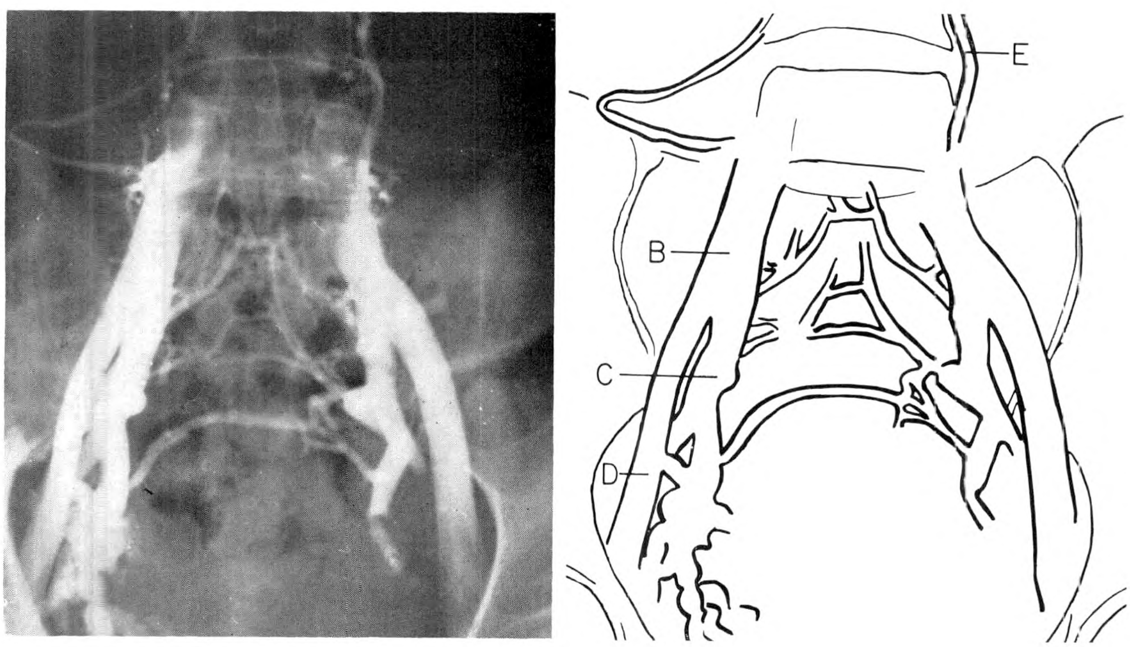
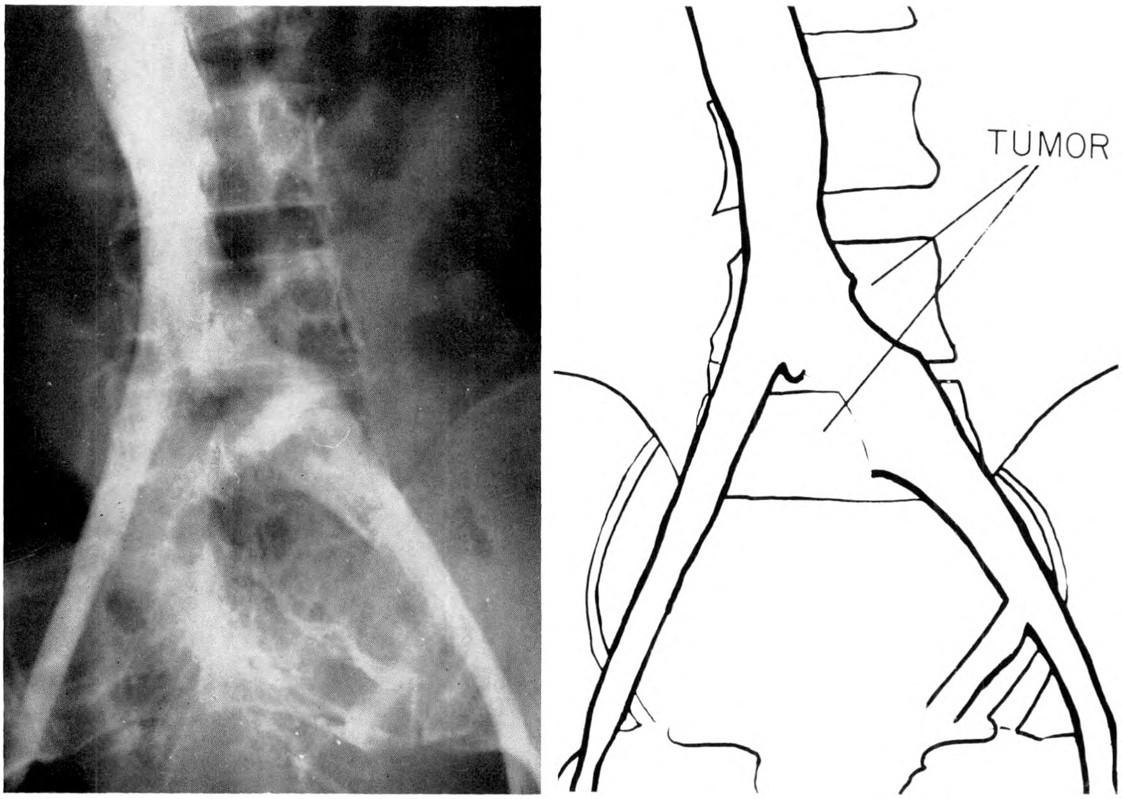


FIG. 2.

Normal pelvic venogram with compression. On the diagram, *B*—right common iliac vein, *C*—hypogastric vein, *D*—external vein, *E*—ascending lumbar veins. Asymmetric reflux with a "varicocele" on the right and a well-defined competent valve on the left is demonstrated.


TUMOR

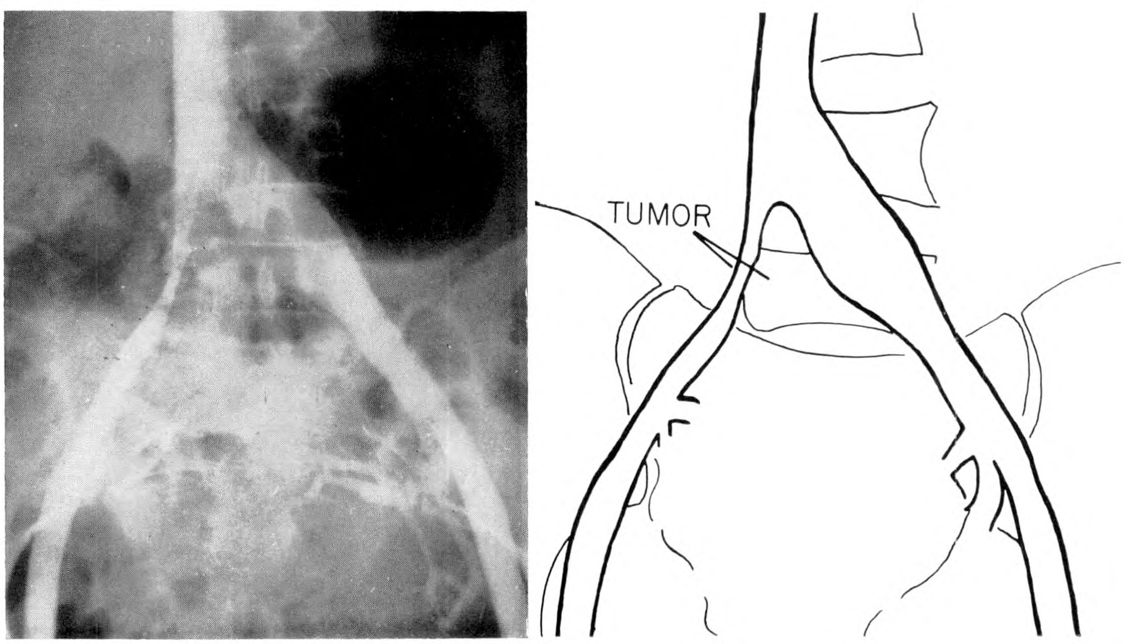

TUMOR

Fig. 3.

This fifty year old patient was diagnosed as having carcinoma of the cervix, LON III and she received radium and parametrial Au^{198} therapy. Microscopic examination of the lymph nodes after extraperitoneal lymphadenectomy did not show metastatic cancer. Six months later the patient returned with bilateral parametrial masses. There was no pain or leg edema.

A venogram made without compression demonstrates scalloped defects surrounding the left common iliac vein and the adjacent vena cava.

At operation a large tumor mass was found about the lower vena cava and left common iliac vein. Biopsy revealed metastatic epidermoid carcinoma.

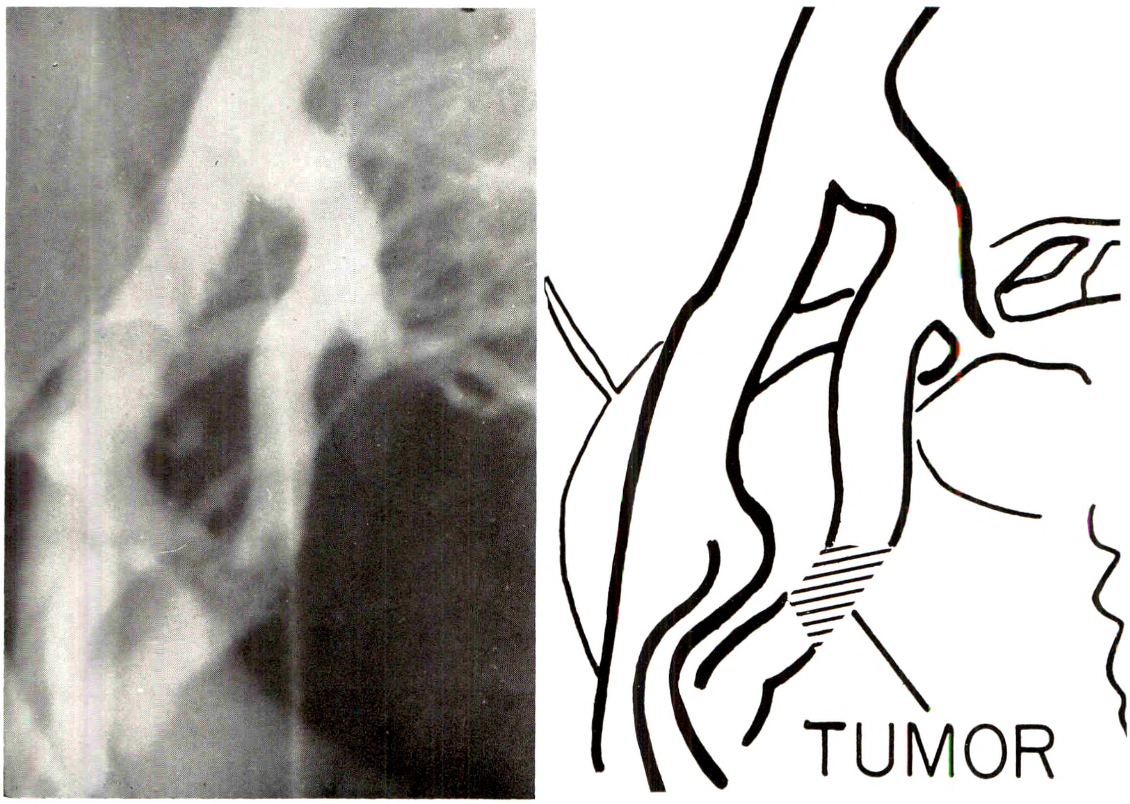


Fig. 5.

Venogram of a patient with a diagnosis of carcinoma of the cervix, LON III, which shows distortion and a pressure defect of the right hypogastric vein.

This patient received radium and parametrial Au^{198} therapy. At lymphadenectomy, a 2.5 cm. lymph node was found adjacent to the hypogastric vein 5 cm. proximal to its junction with the external iliac vein. Microscopic examination showed metastatic epidermoid carcinoma.

Fig. 4.

In 1950 this thirty-three year old female was treated with radium and roentgen therapy (dosage unknown) for carcinoma of the cervix. Nine years later a mass was palpated at the brim of the pelvis, on the right side. There was no leg pain or edema.

Circumferential narrowing of the right common iliac vein immediately caudal to the vena cava is seen on the venogram.

At laparotomy a 1 cm. lymph node was found between the iliac artery and ureter. Microscopic section of this mass revealed metastatic epidermoid carcinoma.

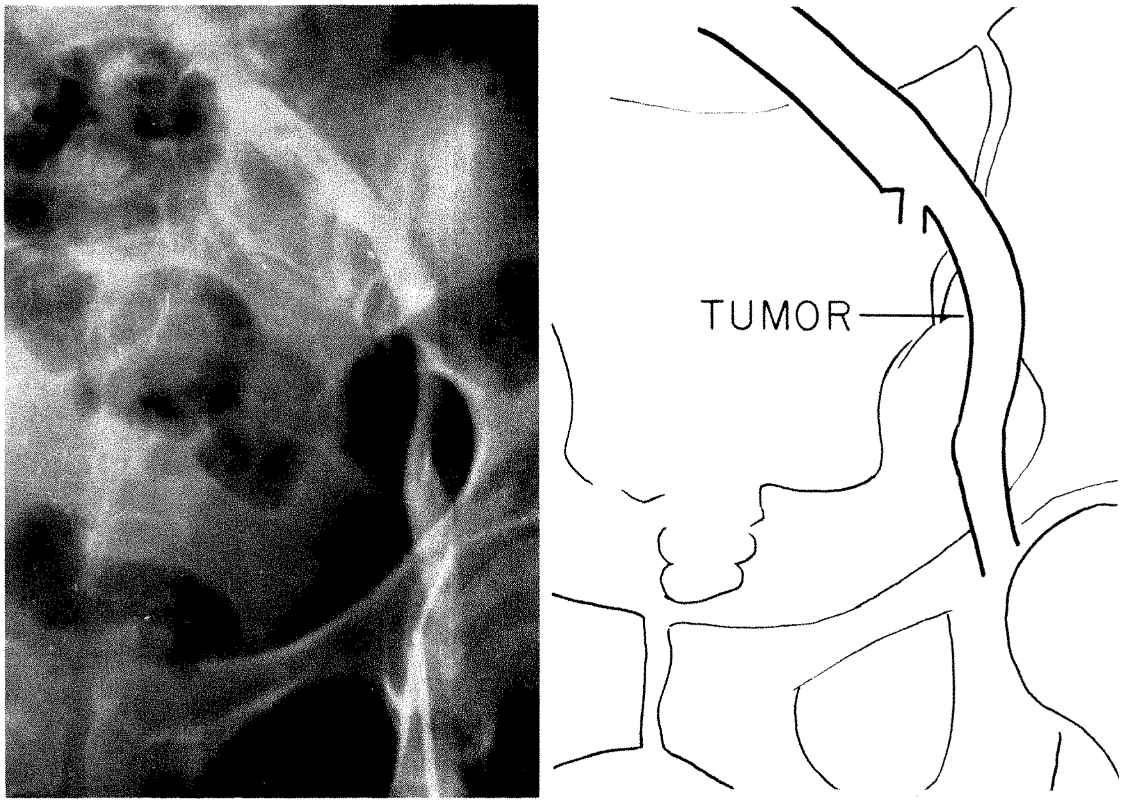


FIG. 6.

Venogram of a fifty-six year old female with carcinoma of the cervix, LON III, demonstrates displacement of the left external iliac vein with lateral bowing. There is no reflux into the left hypogastric vein.

The patient was treated with radium and parametrial Au^{198}. At the time of extraperitoneal lymphadenectomy, firm lymph nodes, 2 cm. in diameter, which were positive for epidermoid carcinoma, lay at the bifurcation of the common iliac vein.

of deficiency of flow in the normal direction or failure of retrograde filling (Fig. 6, 7 and 8). Thrombosis and periphlebitis may cause nonfilling of a part of the vein but it is uncommon and is not associated with other venographic manifestations of a mass lesion. The absence of reflux into one internal iliac vein when it is present on the opposite side, or marked asymmetry of the reflux level without demonstration of a valve and without evidence of a thrombus, is a definite sign of tumor.

(3) *Displacement of a vein* (Fig. 6). In Helander and Lindbom's[8] series displacement was quite uncommon, although it is certainly difficult to estimate.

(4) *Contrast filling of abnormal anastomoses* (Fig. 8). Without findings of the three changes listed above, abnormal anastomoses are only suggestive of venous obstruction by metastatic nodal compression.

RESULTS

It has been the practice in this hospital to perform an extraperitoneal lymphadenec-

→

FIG. 8.

Six months following radium and parametrial Au^{198} therapy for carcinoma of the cervix, LON III, this patient developed obstruction of the left ureter. A nephrectomy was done and the pelvis was found to be free of tumor. One year after the initial therapy she developed left hip pain and a palpable left pelvic mass.

This venogram shows an extreme example of collateral circulation that developed following tumor obstruction of the iliac veins. The veins outline a huge pelvic and lower abdominal mass. The patient was explored and a large necrotic epidermoid carcinoma was found surrounding the vessels.

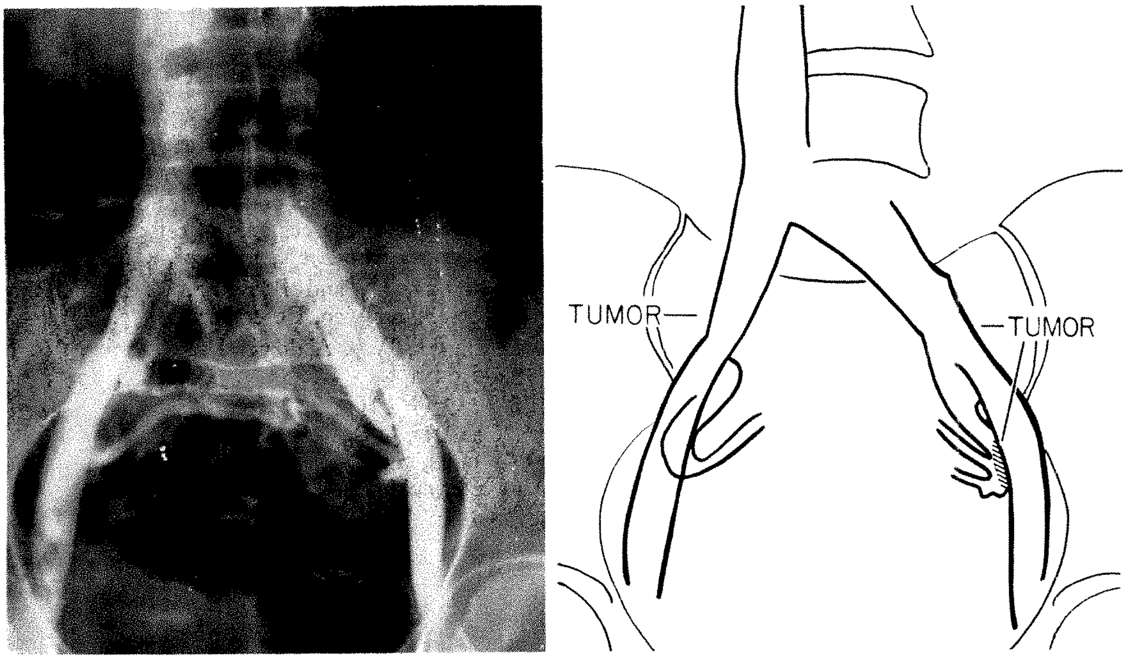
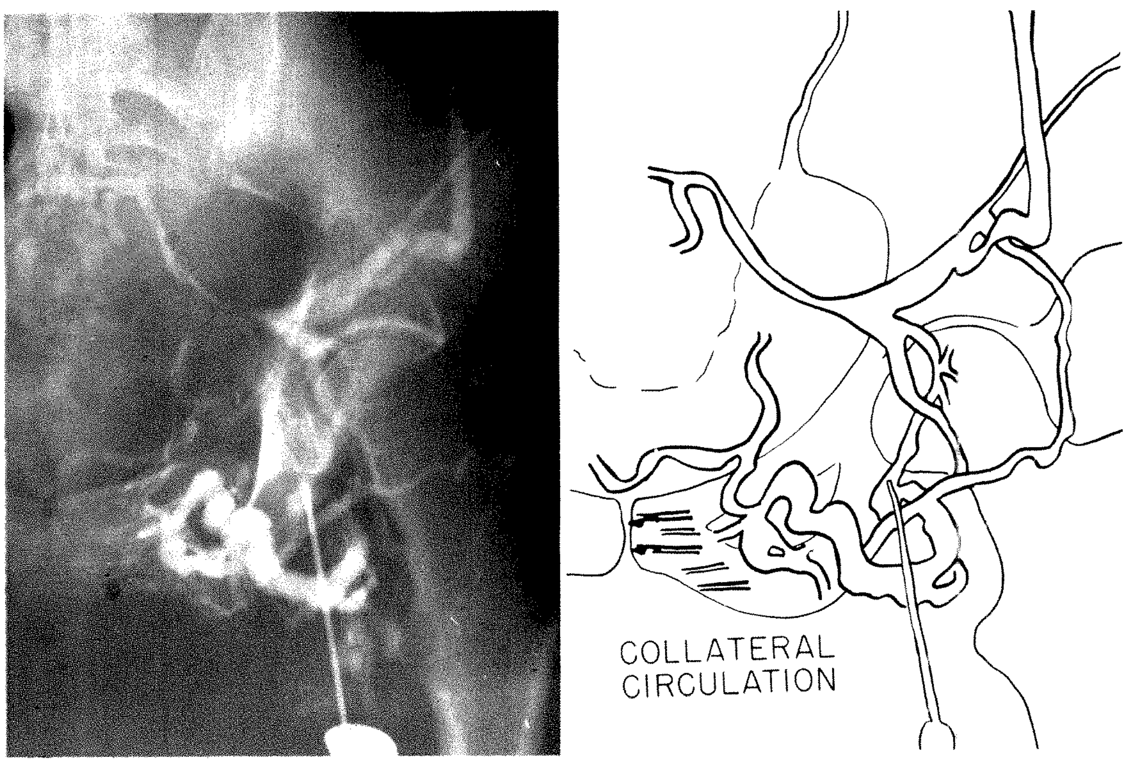


Fig. 7.

A diagnosis of carcinoma of the cervix, LON II, was made on this forty-seven year old woman, and she was treated with radium and parametrial Au^{198}.

The venogram demonstrates indentations on the left common iliac, left external iliac, left hypogastric and right common iliac veins due to lymph nodes with metastatic carcinoma.



tomy after completion of radiation therapy on those patients with LON III carcinoma of the cervix.[16] Initially, venography was performed on these patients after completion of the radiation therapy so that correlation with the pathology would be accurate. At present the roentgen examination is made before the initiation of any therapy, and if there are demonstrable abnormalities in the venous system these patients have repeat venograms before lymphadenectomy.

In our series of 23 proved cases, 14 had no distortion of the venous system. In 13 of these 14 cases, there was no gross or microscopic evidence of tumor in any of the lymph nodes. In 1 case a microscopic focus of cancer was found in a small lymph node. In the 9 proved cases with abnormal venograms, 7 had gross and microscopic evidence that confirmed our findings. The other 2 patients received radium and betatron therapy after the venographic demonstration of metastases and subsequent lymphadenectomy, which showed enlarged lymph nodes at the site of the distortion. Histologic examination revealed marked irradiation effect without evidence of tumor.

CONCLUSIONS

1. Pelvic venography is a safe and accurate procedure.

2. Lymph node metastases can be demonstrated by this technique.

3. Excretory pyelograms can be obtained with this same procedure.

4. Pelvic venography is a satisfactory method to study: (a) the frequency of lymph node involvement, (b) the frequency of the eradication of these lymph nodes by irradiation, and (c) the dosage necessary.

In these ways it promises to be of value in the determination of therapeutic regimes for carcinoma of the cervix.

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THE USE OF A VAGINAL APPLICATOR AS AN ADJUNCT TO THE TREATMENT OF CARCINOMA OF THE CERVIX*

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MOST commonly employed cervical applicators and external therapy techniques for treatment of carcinoma of the cervix do not deliver an adequate dose to the significant vaginal extensions of this tumor. A tubular applicator is the time-honored answer to this problem.[1] Until recently it has been used in our department in the form of a tubular source inside a wooden cylinder. The original description of our particular design was published in 1956.[2] This wooden applicator had the advantage of simplicity of design; however, it had to be covered at each application with a rubber sheath; and it lacked stability, durability, and some of the safety features incorporated in our present model. The new applicator, of all metal construction, can be autoclaved, does not need a rubber sheath, and requires less handling, thus reducing exposure to personnel.

DESCRIPTION

The applicator (Fig. 1) consists of a hollow aluminum cylinder with over-all dimensions of 8.5 cm.×3 cm. with an outside wall thickness of approximately 2 mm. The central cylinder, which holds the low intensity cobalt capsules, is bored exactly to fit their outside diameter and has a wall thickness of 2 mm. A set screw is employed to close the central cylinder once it is loaded. A 20 cm. handle is available with which to grasp the applicator after loading.

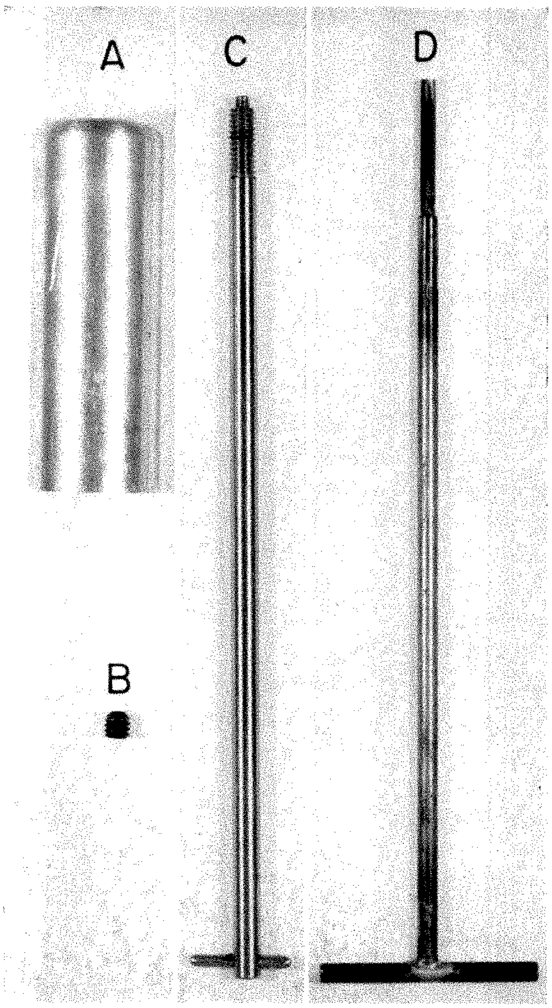

Fig. 1. The disassembled applicator consisting of: A, tube; B, set screw; C, handle; D, wrench for removing set screw.

INDICATIONS

We have elected to use the above described applicator in any carcinoma of the cervix with vaginal extension beyond the upper one third of the vagina. In addition to our usual work-up for carcinoma of the

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cervix, each patient is cystoscoped, urethroscoped, and proctoscoped to determine any invasion of these adjacent organs by the vaginal extension. The discovery of such involvement does not contraindicate the use of this applicator; however, it does increase the incidence of fistulae in the corresponding organ.

METHOD

The applicator is usually inserted concomitantly with urethroscopy and cystoscopy. Once the bladder, rectum, and urethra have been evaluated, the cylinder is introduced into the vagina by means of the metallic handle. Most vaginas readily accommodate the applicator and in very few patients are relaxing incisions necessary. Two or three sutures are used to approximate the labia majora. The handle is then unscrewed from the cylinder. A Foley type catheter containing 5 cc. of 5 per cent NaI is left in place in the bladder.

The position of the applicator is checked in each case with pelvic roentgenograms using a radiopaque medium in a Foley bag and barium in the rectum (Fig. 2, *A* and *B*). It is desirable to place a metal skin clip on the vagina at the point of lowest extension of the tumor, as well as on the lip of the cervix.

DOSAGE

Low intensity, full and half-strength cobalt 60 capsules are used in the cylinder. They are of the stainless steel type with an over-all diameter of 3 mm., wall thickness of 0.5 mm., over-all length 1.6 cm., and an active length of 1.0 cm. Their strengths at this time are approximately 8 and 4 mc. Four capsules are loaded into the applicator according to the dosage pattern desired (Table I and Fig. 3). In actual clinical practice the "ideal" distribution is most frequently employed. The loaded applicator is allowed to remain in the vagina for approximately five to six days to deliver 6,000 r_γ to the surface.

The dose to various points about the applicator may be obtained for various dosage patterns by multiplying the total mc dose by the appropriate factor in Table I. This table was calculated from cumulative summations of each source, neglecting absorption of the aluminum, but including self absorption by the capsules.

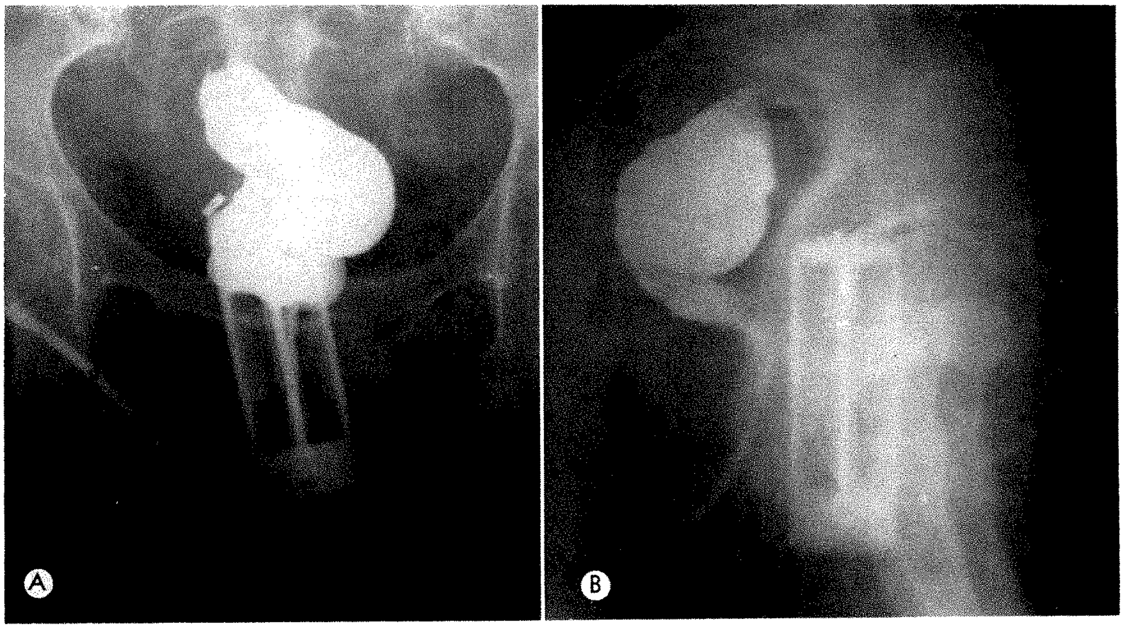

FIG. 2. Typical (*A*) anteroposterior and (*B*) lateral pelvic roentgenograms.

TABLE I

DOSAGE CALCULATIONS FOR THE APPLICATOR LOADED WITH FULL AND HALF STRENGTH COBALT 60 CAPSULES IN VARIOUS PATTERNS*

Loading	Points												
	A	B	C	D	E	F	A′	B′	B″	C′	D′	E′	F′
Uniform	2.03	1.40	2.46	3.01	3.01	2.46	.62	.58	0.82	1.19	1.45	1.45	1.19
End Load	3.10	1.83	3.08	2.95	2.61	2.06	.91	.69	.98	1.36	1.45	1.32	1.04
Double End Load	2.68	1.73	3.02	3.39	2.63	1.89	.81	.68	.97	1.38	1.55	1.34	.99
Ideal Load	2.59	1.58	2.65	2.63	2.63	2.65	.79	.61	1.87	1.21	1.34	1.34	1.21

* Total mc of the capsules × appropriate factor above = r per hour at point x.
= is one full strength capsule.
– is one half strength capsule.

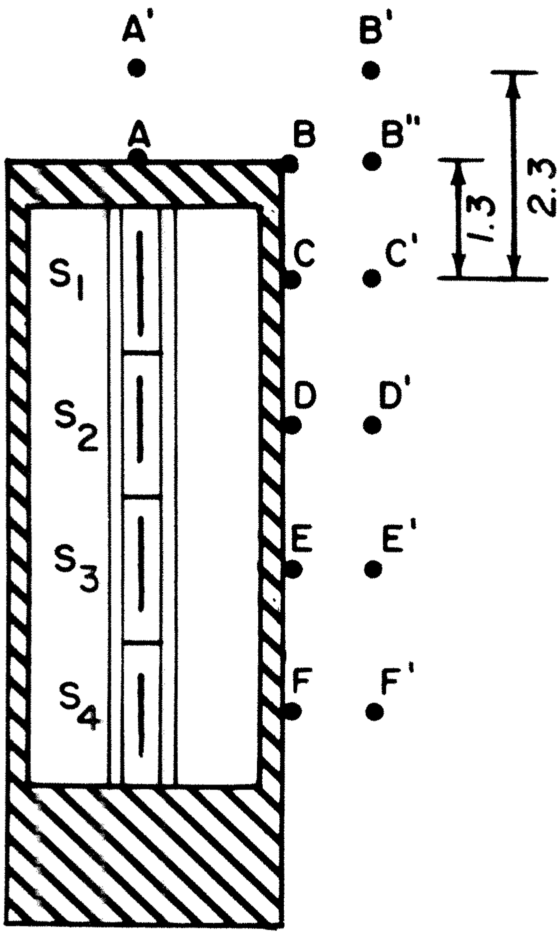

FIG. 3. Cross-sectional drawing of applicator with points corresponding to those in Table I. Points A through F are on the surface of the applicator. Points A′ through F′ are 1 cm. from the surface.

In the usual application, the posterior bladder and the anterior rectal serosa receive no more than 50 per cent of the dosage administered to the surface of the applicator, due to the rapid fall-off, and that dosage is to only a narrow strip. Difficulty with excessive dosage to the bladder and rectum may be encountered by combining this type of application with some techniques of external therapy, but not with the traditional, separated, straight-on anterior and posterior pelvic fields. We have found that such an application does not interfere with the use of the usual tripartite applicator. The areas where the dose patterns may overlap are the fornices and cervix, which are relatively radioresistant in clinical practice. Thus far, in our experience, the applicator has not significantly raised the incidence of complications in the treatment of carcinoma of the cervix.

DISCUSSION

We believe that the above described applicator is a useful adjunct in the treatment of carcinoma of the cervix with vaginal extension, and find this technique practical and applicable in the great majority of these cases. It is uncommon in our experience for a case to require an individual mold.[3] Other sizes of this model are planned for the exceptional cases we may encounter in the future.

SUMMARY

A description of an aluminum "broomstick" vaginal applicator for use in the treatment of vaginal extension of carcinoma of the cervix is given. Indications and techniques for its use are discussed.

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COBALT 60 TUMOR TREATMENT TIME AND "SKIN" DOSAGE CHARTS*

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IN THE treatment of tumors with cobalt 60 teletherapy units, the skin dose is no longer a limiting factor in delivering a sufficient dose to the tumor, especially when two or more ports are used. Therefore, tables which give the time of treatment for 100 r, at various depths in tissue, are useful. It is also desirable to know the dose which the skin receives during this treatment time. The "skin" dose is the maximum dose received at about 6 mm. below the surface where electron equilibrium is established.

These figures are given in Table I, a treatment time and "skin" dosage chart for 80 cm. source skin distance (S.S.D.). The time in minutes to give 100 r at a depth is charted against that depth for the given field size. The "skin" dose for the number of minutes the patient is exposed, listed in the column headed "Min.," is given in the adjoining column headed "Max. r". For example, if the center of the tumor is 7 cm. below the surface and the field size is 200 sq. cm., it will take 5.14 minutes to give 100 r to this depth. The Max. r 0.6 cm. below the skin or so called "skin" dose will be 141 r. The time has been kept in minutes, tenths and hundredths of a minute instead of minutes and

TABLE I

TREATMENT TIME AND "SKIN" DOSAGE CHART

80 cm. S.S.D.

Time in minutes to give 100 r tumor dose at depth and "skin" dose, Max. r, for 100 r at depth

Output 27.2 r/min. at 80 cm. S.S.D.

Depth in cm.	Area in sq. cm.									
	25		50		100		200		400	
	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.
0.6	100	3.72	100	3.72	100	3.65	100	3.63	100	3.63
2.0	108	4.01	107	3.97	107	3.90	107	3.88	107	3.88
3.0	116	4.29	114	4.22	112	4.10	113	4.07	111	4.05
4.0	124	4.58	122	4.51	119	4.38	119	4.32	117	4.27
5.0	134	4.96	131	4.84	127	4.65	125	4.55	123	4.48
6.0	144	5.37	143	5.25	136	4.97	133	4.84	131	4.70
7.0	156	5.80	150	5.55	146	5.32	141	5.14	139	5.04
8.0	169	6.25	162	5.99	157	5.75	151	5.49	147	5.34
9.0	183	6.77	174	6.43	167	6.11	161	5.74	156	5.66
10.0	198	7.10	181	6.72	179	6.55	173	6.22	165	6.02
11.0	214	7.96	203	7.52	192	6.91	184	6.70	177	6.25
12.0	231	8.54	220	8.13	206	7.55	197	7.13	188	6.81
13.0	252	9.46	236	8.75	222	8.13	210	7.60	199	7.13
14.0	271	10.01	256	9.46	239	8.77	225	8.14	212	7.73
15.0	293	10.82	275	10.20	257	9.44	249	8.65	227	8.16

* From the Radiation Therapy Department of the Presbyterian Hospital in Newark, New Jersey, a unit of the United Hospitals of Newark.

seconds because it is easier to multiply this figure by multiples of 100 r to compute the time for the required dose. The faces of the control timers can be graduated in minutes, tenths and hundredths of a minute. This obviates the need to transpose into minutes and seconds, a general source of error in calculation.

In these computations no allowance has been made for the change of output in air with field size. The output which has been usedis that for a 10×10 cm. field. The difference between this and the output for other fields is less than 5 per cent. The 0.6 cm. depth is considered as if it were at the source skin distance of 80 cm. Allowance, however, has been made for backscatter. The times have been calculated by using depth dosage data of Johns, Epp, Cormack and Fedoruk.[1] If one wanted a more accurate table, the actual output for the given field size could be used in the calculation.

Table I makes it very easy to determine the time for a required tumor dose at a given depth and to find the "skin" dose without having to do the calculation from depth dose tables each time.

Similar tables have been calculated for a S.S.D. of 50 cm. (Table II) and 100 cm. (Table III). The 100 cm. distance is used with one of our Co^{60} machines when a field dimension larger than 20 cm. is needed, as in the supraclavicular field for breast work on a large patient.

The "skin" dose as listed in these tables remains the same for all machines used at the given distance, since this depends only on the depth dose for the given field size. This is so because the dose that the "skin" receives when 100 r is delivered to the specified depth depends only on the per cent depth dose and depth dose is independent of type of machine. Of course, the depth dose varies with the source skin distance

Table II

TREATMENT TIME AND "SKIN" DOSAGE CHART

50 cm. S.S.D.

Time in minutes to give 100 r tumor dose at depth and "skin" dose, Max. r, for 100 r at depth
Output 43.3 r/min. at 50 cm. S.S.D.

Depth in cm.	Area in sq. cm.									
	20		50		100		200		400	
	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.
0.5	100	2.32	100	2.32	100	2.30	100	2.26	100	2.26
1.0	104	2.40	103	2.38	103	2.34	102	2.32	102	2.32
2.0	112	2.57	110	2.52	109	2.49	109	2.46	108	2.45
3.0	122	2.80	119	2.74	117	2.69	116	2.64	115	2.60
4.0	132	3.04	128	2.94	126	2.86	124	2.80	123	2.78
5.0	144	3.30	138	3.17	135	3.10	133	2.99	131	2.94
6.0	157	3.60	150	3.44	146	3.34	143	3.20	139	3.15
7.0	171	3.94	163	3.76	158	3.58	153	3.45	149	3.37
8.0	188	4.30	178	4.07	171	3.90	164	3.72	160	3.58
9.0	206	4.73	194	4.44	186	4.13	178	4.05	170	3.84
10.0	225	5.15	211	4.86	201	4.59	191	4.32	182	4.12
11.0	247	5.63	230	5.27	218	4.98	207	4.67	195	4.42
12.0	270	6.17	250	5.74	237	5.43	222	5.00	209	4.70
13.0	295	6.79	272	6.25	256	5.85	240	5.27	224	5.06
14.0	322	7.39	297	6.81	278	6.35	259	5.80	240	5.41
15.0	351	8.08	324	7.44	301	6.87	278	6.26	256	5.78

TABLE III

TREATMENT TIME AND "SKIN" DOSAGE CHART
100 cm. S.S.D.

Time in minutes to give 100 r tumor dose at depth and "skin" dose, Max. r, for 100 r at depth
Output 17.4 r/min. at 100 cm. S.S.D.

Depth in cm.	Area in sq. cm. 200		400	
	Max. r	Min.	Max. r	Min.
0.6	100	5.80	100	5.80
1	101	5.87	101	5.87
2	106	6.15	105	6.13
3	111	6.43	110	6.39
4	116	6.75	115	6.68
5	123	7.12	121	7.04
6	129	7.50	128	7.42
7	137	7.95	134	7.80
8	145	8.42	142	8.22
9	154	8.95	150	8.69
10	165	9.59	159	9.25
11	176	10.20	168	9.75
12	187	10.85	178	10.30
13	198	11.53	189	10.97
14	212	12.25	200	11.61
15	225	13.02	212	12.35
16	239	13.89	225	13.03
17	255	14.78	238	13.79
18	272	15.73	252	14.61
19	289	16.77	267	15.49
20	307	17.78	282	16.34

Note: Calculated by inverse square law from 80 cm. S.S.D.

and field size. The time to deliver the 100 r to a specified depth will depend on the output of the machine and therefore will vary from one machine to another. But once the 100 r is delivered the skin dose will be the same.

The time in minutes for any cobalt 60 machine for an 80 cm. S.S.D., depth, and field size can be calculated from that listed in Table I. For example, if a machine at a S.S.D. of 80 cm. has an output of 38.4 r/min., then the time to give 100 r to a depth of 8 cm. for a field size of 50 sq. cm., T_8, of that machine, is to, t_8, of the given chart inversely as the respective outputs.

$$\frac{T_8}{t_8} = \frac{\text{Output on chart}}{\text{Output}}$$

$$\frac{T_8}{5.99} = \frac{27.2}{38.4}$$

$$T_8 = 4.24 \text{ min.}$$

The same method of calculation can be used for the 50 cm. S.S.D. and 100 cm. S.S.D. and when the charts are changed to allow for decay of the cobalt 60.

Treatment time charts have also been compiled for rotation therapy. The average thickness of the patient in centimeters is charted versus the time for delivery of 100 r to the center of rotation (Table IV). The

TABLE IV

ROTATION THERAPY
TREATMENT TIME CHART
55 cm. S.A.D

Time in minutes to give 100 r tumor dose for different thicknesses
Output 35.8 r/min. at 55 cm. S.A.D.

Average Thickness in cm.	Area in sq. cm. 50	100	150	200	400
	Min.	Min.	Min	Min.	Min.
10	3.24	3.14	3.10	3.06	2.97
11	3.31	3.20	3.16	3.10	3.01
12	3.40	3.29	3.22	3.16	3.08
13	3.48	3.35	3.29	3.22	3.14
14	3.59	3.44	3.37	3.31	3.18
15	3.68	3.52	3.44	3.37	3.24
16	3.78	3.61	3.52	3.46	3.31
17	3.88	3.70	3.61	3.54	3.37
18	3.99	3.80	3.70	3.63	3.46
19	4.14	3.88	3.80	3.72	3.52
20	4.23	3.99	3.91	3.80	3.61
21	4.36	4.10	3.99	3.88	3.68
22	4.49	4.21	4.10	3.99	3.76
23	4.64	4.33	4.21	4.10	3.84
24	4.76	4.44	4.31	4.21	3.93
25	4.91	4.58	4.42	4.31	4.02
26	5.04	4.70	4.55	4.42	4.10
27	5.19	4.83	4.65	4.53	4.18
28	5.34	4.98	4.78	4.64	4.27
29	5.50	5.10	4.91	4.76	4.38
30	5.66	5.25	5.04	4.87	4.46

average thickness in centimeters is twice the average depth of the center of rotation or center of the tumor. The reason for using average thickness will be explained shortly. The time of treatment was calculated by using tumor to air, T/A, ratios for the given depth and field size as described by Johns, Morrison and Whitmore.[2]

The skin dose cannot be derived as easily as for fixed beam therapy but may be obtained from Co^{60} isodose curves for rotation.

The times of treatment for any cobalt machine, including source axis distances (S.A.D.) other than 55 cm., may be obtained from Table IV by formulating a proportion similar to that given above for fixed port therapy and using the output at the center of rotation. This is so because the T/A ratios are independent of distance, from 40 cm. to 100 cm.

We have found that less than 4 per cent error is made when the averages of the anteroposterior and lateral dimensions of a patient are used in calculating the T/A ratio, instead of finding the average T/A ratio from those corresponding to the depth of the center of rotation for twelve sectors. This obtains even when the tumor center is not symmetrically situated in the patient. However, this does in no way obviate the necessity of accurately localizing the tumor

Table V

OPPOSING PORT THERAPY
TREATMENT TIME AND "SKIN" DOSAGE CHART
55 cm. S.A.D.

Time in minutes to treat each port, to give 100 r tumor dose from two opposing ports and "skin" dose, Max. r, including exit dose for 100 r at 55 cm. S.A.D.
Output 35.8 r/min. at 55 cm. S.A.D.

Thickness in cm.	Area in sq. cm.									
	50		100		150		200		400	
	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.
10	107	1.62	106	1.57	105	1.55	104	1.53	103	1.49
11	109	1.65	107	1.60	106	1.58	105	1.55	104	1.51
12	111	1.70	109	1.64	108	1.61	107	1.58	106	1.54
13	113	1.75	111	1.67	110	1.64	109	1.61	108	1.57
14	116	1.80	113	1.72	112	1.68	111	1.65	109	1.59
15	118	1.84	116	1.77	114	1.72	113	1.68	111	1.62
16	122	1.89	118	1.81	117	1.77	116	1.73	113	1.65
17	125	1.94	121	1.85	120	1.81	119	1.78	115	1.68
18	129	2.00	125	1.90	123	1.85	122	1.82	118	1.73
19	133	2.06	128	1.94	127	1.90	125	1.86	121	1.77
20	138	2.22	132	1.99	131	1.95	129	1.90	125	1.81
21	143	2.18	137	2.05	135	1.99	133	1.94	128	1.84
22	148	2.24	141	2.11	139	2.05	137	1.99	132	1.88
23	154	2.32	147	2.17	144	2.11	141	2.05	136	1.92
24	160	2.38	152	2.22	149	2.16	146	2.11	140	1.96
25	167	2.46	158	2.28	154	2.21	152	2.16	144	2.00
26	174	2.52	164	2.35	160	2.27	157	2.21	149	2.05
27	181	2.60	171	2.42	167	2.32	163	2.26	154	2.10
28	189	2.67	179	2.49	173	2.40	169	2.31	159	2.14
29	198	2.76	186	2.55	181	2.46	176	2.38	165	2.19
30	208	2.83	195	2.62	189	2.52	184	2.44	181	2.23

and its center. It does make dosage calculation for rotation therapy with Co^{60} simpler and allows charts to be made which can easily be used. A word of warning—the same short cut may not be used for the 200 kv. region. Here errors as large as 20 per cent would occur.

It is often convenient with the patient lying on the treatment table to place the center of the tumor at the center of rotation and treat the tumor through two opposing ports, anterior and posterior, or two lateral ports. Table v is useful for this type of treatment. It gives the treatment time for each of the two ports in order to deliver a tumor dose of 100 r (50 r from each). The "skin" dose includes the exit dose. The "skin" dose remains the same for all cobalt machines with a S.A.D. of 55 cm. and the center of the tumor at the center of rotation. The assumption has been made that the center of the tumor is equidistant between the two surfaces. If the center is slightly asymmetric, the error is not too great. The time of treatment for any machine at a S.A.D. of 55 cm. with a known output may be calculated from the times given in the chart by using the proportion previously given.

These tables have been tested by a number of radiologists who have cobalt 60 machines and were found to be very useful.

SUMMARY

1. Treatment time and "skin" dosage charts for different field sizes are given for 80 cm., 50 cm., and 100 cm. source skin distances. The "skin" dose remains the same for all machines for the given S.S.D., depth, and field size.

2. A treatment time chart for rotation therapy is given in which the time for 100 r is listed versus the average thickness of a patient for different field sizes. This chart is applicable for source axis distances from 40 cm. to 100 cm.

3. A table is given for use with opposing port therapy at 55 cm. S.A.D. The time to treat each port, for 100 r tumor dose, and the "skin" dose including exit dose are charted versus the thickness of the patient for different field sizes.

4. A method is described for calculating the treatment times for any cobalt 60 therapy machine from the given tables.

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FOCUSED GRID TELECOBALT THERAPY*

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A RELATIVELY large number of hopelessly advanced cancer cases are referred to our department of radiotherapy. These patients have such advanced disease that the surgeons cannot undertake removal of the tumor and expect a postoperative survival. A radiotherapist, knowing from experience that conventional treatment with homogeneous radiation does not inevitably alleviate pain and prolong life, dreads the referral of such cases and often refuses to treat them. A course of therapy by conventional methods usually involves four to six weeks of hospitalization or outpatient visits. Toward the end of the treatment, the patient may still suffer considerable discomfort from both the tumor and the effects of treatment. Sorely needed was a practical and efficient method of palliation that would permit the administration of large doses of radiation in a short span of time with minimum side reactions and maximum relief of symptoms. An effective method would make it possible to: (1) deliver large doses of radiation; (2) shorten the treatment period (ten days to two weeks); (3) cause rapid tumor regression; (4) maintain anatomic and physiologic integrity of organs involved; (5) minimize radiation sickness (nausea, vomiting, malaise); and (6) minimize skin reaction.

In searching for a way to accomplish these objectives, we decided at the beginning of 1957 to modify our telecobalt therapy by the use of a grid. The idea was suggested by the observation of some patients who received excellent palliation from 250 kv. peak therapy with grids. An analogy can also be drawn from the effects of radium or cobalt needle implantation.[1,2,3]

Our modification of the conventional telecobalt therapy involves the use of a grid fashioned from a block of lead 5.4 cm. thick which is perforated by cylindrical holes diverging toward the patient. The lead block is attached to the treatment cone, and a perforated piece of metal is attached to the grid to permit registry of the grid pattern with successive treatments (Fig. 1 and 2).

CLINICAL MATERIAL

From May, 1957 through December, 1958, we treated 87 patients with focused grid telecobalt therapy. The youngest patient was three and one-half years of age; the oldest eighty-three. The mean age was fifty-nine years. Forty-six patients were white and 41 were Negro. Forty-nine were

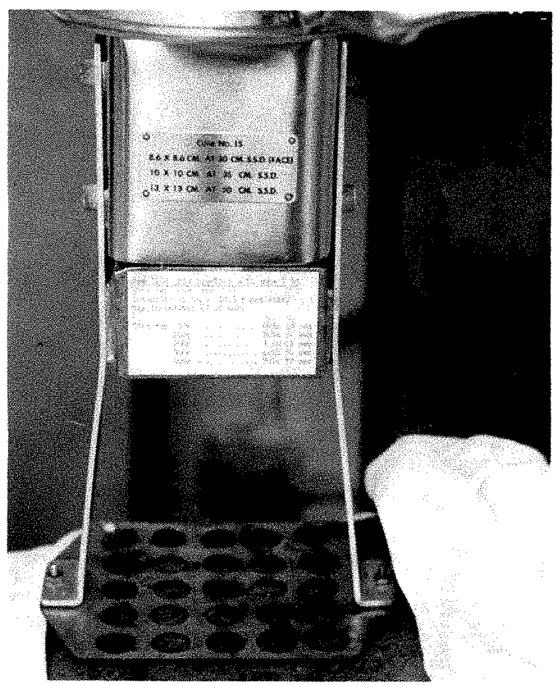

FIG. 1. Focused grid in position for treatment.

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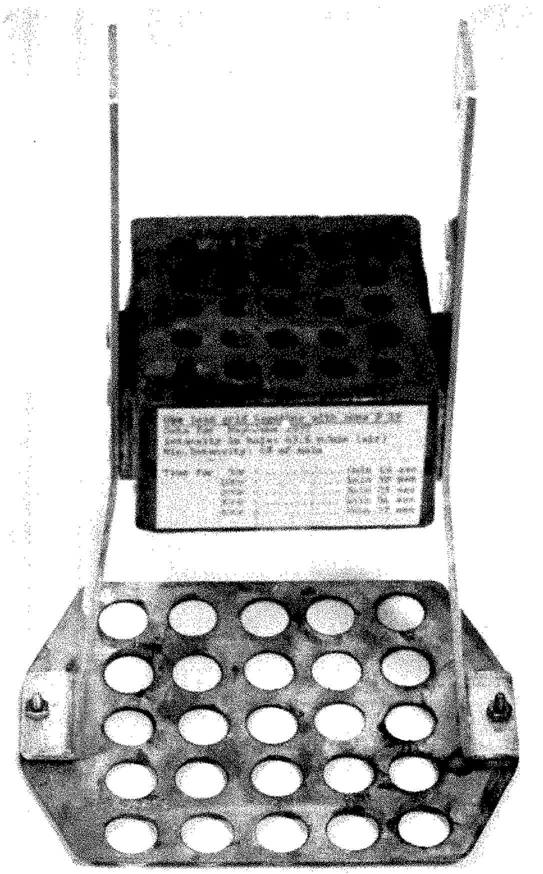

FIG. 2. Detail of focused grid and metal register.

men and 38 women. During the time of this study, 45 patients remained alive and 42 died. There were 18 cases of carcinoma of the bladder, 25 cases of carcinoma of the lung, 20 cases of carcinoma of the female genital tract, 17 cases of carcinoma of the head and neck including 3 cases of carcinoma of the esophagus, and 7 cases of miscellaneous malignancies (Table I). A more detailed breakdown of the number and types of carcinoma treated is given in Tables II, III, and IV.

In order to analyze whether or not relief was obtained from the treatments, a palliation index was devised. The palliation index (PI) is the product of two factors, namely, the palliation factor (P) and the number of months of survival (T).

The palliation factor (P) was designated by four grades of relief ranging from P-0 to P-3. Palliation factor 3 (P-3) meant that the patient had received maximal benefit and was able to conduct his life in a manner similar to his mode of living prior to illness. Palliation factor 2 (P-2) meant that the patient had a good result in terms of considerable alleviation of symptoms and regression in the size of the tumor. Palliation factor 1 (P-1) meant that the patient had received appreciable benefit in terms of alleviation of symptoms, regression of the size of the tumor, or both. No palliation, or P-0, meant that the patient had received no benefit, or may indeed have gotten worse.

To define the palliation factor objectively, it was decided to grade the symptoms and the status by physical examination and by laboratory, roentgenographic, operative, and pathologic findings obtained after completion of therapy. As the findings changed during follow-up, the individual

TABLE I

VITAL STATISTICS

Origin of Carcinoma	No. of Patients	Mean Age (yr.)	Age Range (yr.)	Race		Sex		Living	Dead
				White	Negro	Male	Female		
Bladder	18	65	44–76	11	7	8	10	9	9
Lung	25	58	35–80	17	8	24	1	12	13
Female Genital	20	56	25–83	4	16	0	20	13	7
Head and Neck	17	67	39–82	9	8	12	5	6	11
Miscellaneous	7	51	3.5–74	5	2	5	2	5	2
Total	87	59	3.5–83	46	41	49	38	45	42

TABLE II

FEMALE GENITAL TRACT

Site of Origin	No. of Patients
Carcinoma of Endometrium	9
Carcinoma of Cervix (1 sarcoma and 1 adenocarcinoma)	9
Carcinoma of Ovary	2
Total	20

TABLE IV

MISCELLANEOUS MALIGNANCIES

Site of Origin	No. of Patients
Prostate	1
Colon	1
Hodgkin's Disease	1
Kidney	1
Pancreas	1
Scrotum	1
Lymphosarcoma	1
Total	7

factors were averaged; this resulted in a mean palliation factor which was judged the fairest approximation by conference opinion.

The survival time (T) was calculated in months of survival. If the patient was still living at the end of the time of analysis (December 31, 1958), a plus was included with the palliation index. If the patient was dead at the end of the period of analysis, the palliation index was given without the additional sign.

Analysis of the palliation factor (Table V) reveals that of the 87 patients, 51 (59 per cent) received appreciable palliation or better (P-1, 2 and 3). No palliation was observed in 36 patients (41 per cent). A further breakdown shows that 30 patients (35 per cent) received appreciable relief (P-1) and 12 patients (14 per cent) received good palliation (P-2). Nine patients (10 per cent) had excellent palliation (P-3).

TABLE III

HEAD AND NECK

Site of Origin	No. of Patients
Carcinoma of Pharynx	1
Carcinoma of Tonsil	2
Carcinoma of Oral Cavity	1
Carcinoma of Hard Palate	2
Carcinoma of Floor of Mouth	1
Carcinoma of Buccal Mucosa	1
Carcinoma of Gingiva	1
Carcinoma of Sinuses	2
Carcinoma of Skin	2
Metastases to Neck	1
Carcinoma of Esophagus	3
Total	17

Successful palliation from grid therapy varied considerably with the site of origin of the carcinoma (Table VI). The best palliative results were obtained in carcinoma of the bladder (78 per cent), and the least palliative results in carcinoma of the lung (only 36 per cent benefited). Of the patients who had female genital tract carcinoma, 65 per cent were successfully treated. Of the patients with carcinoma of the head and neck, 59 per cent experienced relief, and 71 per cent of the miscellaneous malignancies were successfully treated.

In terms of human suffering and months of survival, it is noted (Table VII) that there were 101 months of a total of 438 survival months for the entire group without palliation. In other words, 23 per cent of the total months survived can be considered a treatment failure. Thirty patients survived 203 months at the appreciable palliation factor of P-1, yielding a total of 46 per cent of the months survived at this level of palliation. Good palliation (P-2) was achieved in 12 patients for 52 months, 12 per cent of the months survived. Nine patients had excellent palliation (P-3) and survived 82 months, which is 19 per cent of the total months survived. Undoubtedly, in a series with such advanced cases of cancer, even if the patients had survived 438 months without treatment, palliation could hardly be expected. It can be concluded that the focused grid telecobalt

Table V

PALLIATION AND SURVIVAL BY CANCER SITE

Cancer Site	Palliation Factor (P)							
	P-0 None		P-1 Appreciable		P-2 Good		P-3 Excellent	
	No. of Patients	Total Survival (mo.)	No. of Patients	Total Survival (mo.)	No. of Patients	Total Survival (mo.)	No. of Patients	Total Survival (mo.)
Bladder	4	6	9	49	3	12	2	15
Lung	16	37	5	16	4	13		
Female Genital	7	29	8	87	1	1	4	44
Head and Neck	7	24	6	35	3	17	1	5
Miscellaneous	2	5	2	16	1	9	2	18
Total	36	101	30	203	12	52	9	82

Table VI

SUCCESSFUL PALLIATION FROM GRID THERAPY BY CANCER SITE

Cancer Site	Total No. of Patients	Appreciable Palliation or Better (P-1, 2, 3)		Good to Excellent Palliation (P-2, 3)	
		No. of Patients	Per Cent	No. of Patients	Per Cent
Bladder	18	14	78	5	28
Lung	25	9	36	4	16
Female Genital	20	13	65	5	25
Head and Neck	17	10	59	4	24
Miscellaneous	7	5	71	3	43
Total	87	51	59	21	25

therapy was successful in producing some relief of symptoms in 51 patients for 337 months, or 77 per cent of the total time survived.

From Table VI, it appears that patients with cancer of the lung are less likely to receive benefit than those with other types of cancer. Only 9 of 25 patients (36 per cent) with lung cancer received successful palliation, while 14 of 18 persons with bladder cancer (78 per cent) were successfully treated. A low level of success for palliation could militate against the use of focused telecobalt grid therapy in a particular type of cancer. Certainly, if we excluded all the cases of carcinoma of the lung, the palliation results in our series would be strikingly improved. However, from a clinical viewpoint, the physicians in our radiotherapy department consider that even a level of

Table VII

TOTAL SURVIVAL IN MONTHS AND AMOUNT OF PALLIATION

No. of Patients	Palliation	Total Survival	
		Months	Per Cent
36	P-0 (none)	101	23
30	P-1 (appreciable)	203	46
12	P-2 (good)	52	12
9	P-3 (excellent)	82	19
Total 87	Total Months of Survival	438	

appreciable palliation in one-third of the patients with advanced cancer of the lung is worthwhile.

A tabulation of pertinent clinical data by cancer site for individual patients is given in Tables VIII, IX, X, XI, and XII.

From the palliation index (PI), it is easy to recognize patients who received extraordinary benefit and those who received little or none. Following are reports of 3 patients who benefited considerably from this mode of therapy and 3 patients who were treatment failures.

REPORT OF CASES

CASE I. MS 14-60-39. *Transitional Cell Carcinoma of the Bladder.* This sixty-five year old housewife, a patient of Dr. James Headstream, presented with a three months' history that was compatible with cystitis and hematuria. Operation in June, 1957, consisted of fulguration and removal of a portion of a transitional cell carcinoma of the bladder.

On January 7, 1958, she returned for a check-up examination and complained of deep pelvic discomfort with "bearing down sensation." Bimanual examination revealed a large extravesical extension of the tumor on the left.

TABLE VIII

FOCUSED GRID TELECOBALT THERAPY CLINICAL DATA—BLADDER CARCINOMA

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P × T)*	Remarks
1	13-49-03 CC	66 NM	Adenocarcinoma of bladder	III	12,000 r	6/13/57	9/10/57	2	3	6	Ureters transplanted before therapy; pain improved
2	13-05-65 NG	69 WF	Carcinoma of bladder	IV	12,000 r	6/19/57	8/22/57	1	2	2	Tumor showed marked shrinkage
3	13-28-29 PW	74 NF	Adenocarcinoma of bladder	III	2,400 r (incomplete)	7/ 2/57	7/ 5/57	0	0	0	Received only 2 treatments; patient was uremic
4	13-13-54 LW	62 WF	Carcinoma of bladder	III	12,500 r	7/ 9/57		1	17	17+	Tumor recurred but with marked symptomatic improvement
5	13-97-57 EC	66 NF	Adenocarcinoma of bladder	IV	12,000 r	8/30/57	12/15/57	1	3	3	Good relief of pain
6	14-60-39 MS	65 WF	Carcinoma of bladder	III	15,000 r	1/16/58		3	13	39+	Asymptomatic and doing exceptionally well
7	14-86-43 WL	67 WM	Carcinoma of bladder	IV	13,800 r	3/19/58		1	8	8+	Will not return for check-up
8	14-41-76 WN	67 WM	Carcinoma of bladder	IV	12,000 r	3/24/58	9/14/58	1	5	5	Good pretreatment pneumogram
9	11-90-80 MT	76 WF	Carcinoma of bladder	III	12,000 r	4/ 1/58		2	8	16+	
10	08-28-94 JW	73 NM	Carcinoma of bladder	IV	12,000 r	4/ 8/58	8/13/58	1	4	4	Pneumograms on 4/9/58 and 7/1/58 show progression of tumor; since improved
11	15-12-31 NB	71 NF	Carcinoma of bladder	IV	1,000 r (incomplete)	6/ 9/58	9/ 6/58	0	2	0	Incomplete; 1 treatment
12	15-53-04 SC	54 WM	Carcinoma of bladder	IV	12,000 r	8/18/58	12/11/58	1	3	3	
13.	15-50-74 CP	71 NF	Carcinoma of bladder	IV	12,000 r	8/22/58		1	4	4+	Asymptomatic except for slight back pain and dysuria
14	15-50-00 LS	69 WF	Carcinoma of bladder with lung metastases	IV	12,000 r	8/22/58		0	4	0+	Had lung metastases; has good pretreatment pneumogram
15	15-45-55 BK	66 NM	Carcinoma of bladder	IV	12,000 r	9/ 2/58		1	3	3+	
16	15-88-83 DS	44 WM	Carcinoma of bladder	III	12,000 r	11/20/58		3	2	6+	No bleeding, no pain; gained 20 lb.
17	15-97-95 ML	54 WF	Carcinoma of bladder	IV	12,000 r	12/10/58	12/17/58	0	0	0	
18	16-00-35 RH	55 WM	Carcinoma of bladder	IV	12,000 r	12/15/58		2	1	2+	Very mild dysuria, otherwise asymptomatic

* + = patient still living at completion of this study (December 31, 1958).

TABLE IX

FOCUSED GRID TELECOBALT THERAPY CLINICAL DATA—LUNG CARCINOMA

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P XT)*	Remarks
1	13-50-32 JG	67 NM	Carcinoma of lung		12,500 r	5/22/57	8/ 2/57	1	3	3	Therapy interrupted five weeks; post-therapy moderate expansion of left lung
2	13-56-47 JM	56 NF	Adenocarcinoma of lung		4,800 r (incomplete)	6/17/57	6/29/57	0	0	0	Treatment incomplete
3	14-26-28 JB	80 NM	Carcinoma of lung		10,200 r	10/21/57	1/13/58	2	3	6	
4	14-52-82 RC	53 WM	Carcinoma of lung with metastases		12,000 r	1/ 9/58	3/ 6/58	0	2	0	
5	14-44-70 MW	58 WM	Carcinoma of lung		12,000 r	1/16/58	4/ 9/58	0	2	0	Chest roentgenogram showed worsened condition
6	14-31-08 TM	62 WM	Carcinoma of lung		7,500 r (incomplete)	1/20/58		0	11	0+	Chest roentgenogram showed worsened condition; right lower lobe atelectatic
7	14-53-15 JL	61 WM	Carcinoma of lung		15,000 r	1/27/58		0	10	0+	Little relief; Pancoast's syndrome worse (died 3/8/59)
8	14-63-54 RW	57 NM	Carcinoma of lung		15,000 r	2/12/58	4/21/58	1	2	2	No roentgenographic change
9	14-93-74 AS	47 WM	Carcinoma of lung		12,000 r	2/21/58	3/ 6/58	0	0	0	Lived two weeks
10	14-87-01 LT	35 WM	Carcinoma of lung		7,200 r (incomplete)	3/31/58	4/ 8/58	0	0	0	Cancer with abscess formation
11	Ac-08-62 JW	79 NM	Carcinoma of lung		12,000 r	4/ 7/58		1	8	8+	Progression of tumor; pain improved
12	15-01-00 CT	52 WM	Carcinoma of lung		3,000 r incomplete	4/30/58	5/ 3/58	0	0	0	Lived four days; treatment incomplete
13	14-91-52 OE	48 WM	Carcinoma of lung (mesothelial cell)		12,000 r	5/ 5/58	7/14/58	0	2	0	
14	14-97-37 JP	51 WM	Carcinoma of lung		12,000 r	5/12/58		0	7	0+	Much worse, subjectively and objectively
15	14-97-32 JA	71 WM	Carcinoma of lung		12,000 r	7/31/58		2	5	10+	Gained 23 lb.; able to drive car; regression of lesion
16	15-62-91 GB	63 NM	Carcinoma of lung		12,000 r	9/15/58	10/ 3/58	0	0	0	Survived eighteen days
17	15-53-76 CW	53 WM	Carcinoma of lung		10,800 r	9/30/58		2	3	6+	Improved considerably, subjectively and objectively
18	15-59-84 CH	64 WM	Carcinoma of lung		12,000 r	10/ 8/58		1	2	2+	
19	15-75-47 WM	60 WM	Carcinoma of lung		12,000 r	10/17/58		2	2	4+	
20	A2-75-18 CR	60 NM	Carcinoma of lung		4,800 r (incomplete)	10/24/58	11/ 1/58	0	0	0	Incomplete treatment; died in eight days
21	15-82-66 GH	56 WM	Carcinoma of lung		12,000 r	11/20/58		0	1	0+	Simulated abscess of lung (died 1/29/59)
22	15-60-46 HP	63 WM	Carcinoma of lung		12,000 r	11/24/58		0	1	0+	Roentgenograms showed worsened condition
23	15-92-20 CJ	52 WM	Carcinoma of lung		3,600 r (incomplete)	12/ 5/58	12/14/58	0	0	0	Incomplete treatment; died after nine days
24	15-83-28 FW	46 NM	Carcinoma of lung		12,000 r	12/12/58		0	1	0+	Died 2/16/59
25	15-86-22 SS	62 WM	Carcinoma of lung		12,000 r	12/29/58		1	1	1+	Marked reduction in size of mass

* See footnote to Table VIII.

Table X

FOCUSED GRID TELECOBALT THERAPY CLINICAL DATA—FEMALE GENITAL TRACT

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P ×T)*	Remarks
1	A4-43-03 FW	52 NF	Carcinoma of cervix	III	11,200 r	5/24/57		1	19	10+	Biopsy 11/3/57; irradiation; no tumor; gained 43 lb.; ?recurrence 2/17/58
2	13-48-62 RA	37 NF	Adenocarcinoma of cervix	IV	12,000 r	5/27/57	9/23/57	0	4	0	Lower abdominal discomfort
3	13-52-32 DF	70 WF	Adenocarcinoma of uterus		12,000 r	6/10/57		3	19	57+	½ cm. polyp of endometrium; no gross tumor seen; radiation reaction; did well, remained asymptomatic; hysterosalpingo-oophorectomy 8/23/57
4	13-70-99 RR	32 NF	Carcinoma of cervix	III	12,000 r	6/24/57	5/13/58	0	11	0	Surprisingly little tumor found at operation; viable tumor in specimen; anterior evisceration 9/16/57
5	13-65-54 GG	62 WF	Adenocarcinoma of uterus		12,000 r	7/1/57		3	18	54+	From December '57 to January '59 no symptoms; viable, probable adenocarcinoma two months after therapy; hysterectomy 9/13/57
6	13-96-10 MJ	66 NF	Adenocarcinoma of uterus	IV	10,800 r	8/19/57	7/4/58	1	11	11	Chest metastases when treated; massive carcinomatosis found in peritoneal cavity at operation; operation Memphis 11/28/57
7	14-22-49 VB	28 NF	Carcinoma of cervix	IV	12,000 r	10/15/57	2/20/58	0	4	0	No response; roentgenograms showed worsening condition
8	14-14-87 MY	65 NF	Adenocarcinoma of uterus		12,000 r	10/22/57		1	15	15+	Wertheim's operation 1/27/58
9	14-45-25 AN	42 NF	Carcinoma of cervix	IV	13,000 r	12/16/57	6/3/58	1	6	6	Wertheim's operation; grid therapy on right, homogeneous beam on left
10	14-69-43 JB	50 NF	Carcinoma of cervix	IV	19,000 r	2/10/58		1	11	11+	9/2/58. No complaints; obvious tumor present
11	14-66-36 LM	44 NF	Carcinoma of cervix	IV	15,000 r	2/18/58		1	11	11+	Aortic lymph nodes involved; improved considerably but no recent follow-up
12	14-80-00 EP	50 NF	Carcinoma of cervix	IV	12,000 r	3/10/58		1	9	9+	Grid therapy on right side, homogeneous beam on left side
13	14-89-01 WG	83 NF	Adenocarcinoma of uterus		12,000 r	4/7/58		0	6	0+	8/18/58. Swollen feet; granular bleeding lesion on vagina; cancer still present
14	15-09-69 WL	63 NF	Carcinoma of ovary		12,000 r	6/16/58	10/15/58	0	4	0	
15	15-42-07 NM	67 NF	Carcinoma of cervix	IV	12,000 r	8/11/58		1	5	5+	Abdominal bloating; fistula between rectum and vagina 11/17/58
16	15-19-84 MN	81 WF	Adenocarcinoma of uterus		12,000 r	9/2/58		3	4	12+	Feels well; vagina stenotic, cervix firm
17	A7-47-33 CM	25 NF	Carcinoma of ovary with metastases to liver and spleen		9,600 r (incomplete)	9/15/58		0	0	0+	Patient did not return for completion of treatment
18	15-42-00 LW	70 NF	Adenocarcinoma of uterus		12,000 r	10/27/58		3	3	9+	4/8/59. No symptoms; excellent condition; large fibroids were found at operation, radical hysterectomy
19	15-72-65 CM	75 NF	Carcinoma of pelvis; probably adenocarcinoma of uterus		12,000 r	12/1/58	12/10/58	0	0	0	Died in nine days
20	15-94-00 MS	58 WF	Sarcoma of cervix		12,000 r	12/8/58		2	1	2+	Pain in rectum; biopsy, cervicitis, no tumor excellent regression of mass

* See footnote to Table VIII.

TABLE XI

FOCUSED GRID TELECOBALT THERAPY

CLINICAL DATA—HEAD AND NECK CARCINOMA

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P ×T)*	Remarks
1	A5-84-46 AP	76 NM	Carcinoma of pharynx		12,000 r	12/ 5/58	12/18/58	0	0	0	Patient died before completion of therapy
2	A3-41-92 BF	71 NM	Carcinoma of tonsil		12,000 r	2/14/58		1	11	11+	Died 2/8/59
3	13-68-32 PP	71 WM	Carcinoma of tonsil		5,600 r (incomplete)	9/23/58	11/10/58	0	2	0	
4	15-62-41 WC	66 WM	Carcinoma of hard palate		12,000 r	9/10/58		2	3	6+	Extension into sinuses; residual tumor present but no complaints
5	15-95-68 AP	59 NF	Carcinoma of hard palate		12,000 r	12/ 1/58		0	1	0+	Very resistant tumor; no response
6	15-34-22 BB	75 NM	Carcinoma of floor of mouth		11,000 r	7/21/58	8/20/58	0	1	0	Survived one month
7	14-67-95 RW	73 WF	Carcinoma of buccal mucosa		10,000 r	5/ 8/58	10/ 4/58	1	5	5	Retreatment after conventional therapy
8	14-71-98 NG	67 NM	Carcinoma of gingiva		3,000 r (incomplete)	3/ 3/58	4/20/58	0	1	0	Mandible invaded
9	14-55-54 EW	73 NF	Carcinoma of maxillary sinus		12,000 r	1/ 9/58		0	12	0+	Temporary regression of huge mass
10	14-43-93 TH	68 WM	Carcinoma of maxillary sinus		12,000 r 12,000 r	12/10/57 4/ 7/58	5/12/58	2	6	12	Remarkable visible and roentgen improvement
11	14-37-43 MS	82 WM	Skin carcinoma on face		8,000 r	3/11/58	8/24/58	3	5	15	Dramatic response
12	15-06-92 CS	58 WM	Basal cell carcinoma of ear		12,000 r	5/12/58		2	8	16+	Excellent initial result; recurrence in December, 1958
13	13-24-93 HF	39 NF	Anaplastic carcinoma, metastasis to neck		12,000 r	2/10/58	9/14/58	0	7	0	Probably pelvic primary; lymphangitis lung spread, metastatic to brain
14	14-95-37 VT	59 WM	Carcinoma of oral cavity		12,000 r	4/21/58	7/20/58	1	3	3	
15	13-75-48 EH	56 NM	Carcinoma of esophagus		12,000 r	6/ 4/57	11/24/57	1	6	6	
16	13-75-89 BB	58 WM	Carcinoma of esophagus		12,000 r	7/24/57	10/25/57	1	3	3	Remarkable objective improvement on roentgenograms
17	15-08-45 EB	80 WF	Carcinoma of esophagus		12,000 r	6/ 4/58		1	7	7+	Cervical esophageal carcinoma; tumor regressed; follow-up

* See footnote to Table VIII.

Cystoscopy showed that the left lateral and posterior bladder wall was involved by infiltrating tumor. On microscopic examination, the cells were seen to be highly anaplastic. She was referred for grid therapy.

The following factors were used: Keleket-Barnes telecobalt apparatus; half value layer 12 mm. Pb; 50 cm. skin source distance; field size with grid 13×13 cm.; 1 anterior pelvic portal. From January 16 to 29 the patient received 1,500 r each day to a total of 15,000 r as measured in air in the hole center.

At the conclusion of her treatment there was no definite change, but within a month the symptoms disappeared and the urine was clear. In subsequent follow-up examinations, the patient was considered to be in excellent health without evidence of recurrence (P-3, T-12, PI-36+).

CASE II. BB 13-75-89 WM 59. *Epidermoid Carcinoma of the Esophagus.* On July 24, 1957, this patient was referred from the State Mental Hospital with a history of chronic cough, weight loss, fever of unknown origin, and general debility. He was suspected of having tuberculosis. It was noted on the ward that he was refusing food and on several occasions had difficulty in swallowing. Regurgitation was also noted. Except for emaciation and fever, the physical examination was nonrevealing. A barium swallow examination showed carcinoma

TABLE XII

FOCUSED GRID TELECOBALT THERAPY
CLINICAL DATA—MISCELLANEOUS NEOPLASMS

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P×T)*	Remarks
1	13-05-90 JC	54 NM	Carcinoma of prostate, bone metastases		4,800 r (incomplete)	7/ 9/57	9/ 7/57	0	2	0	Insufficient therapy to evaluate grid
2	A7-26-18 AB	70 WF	Adenocarcinoma of colon		12,000 r	10/22/57		1	14	14+	Lymph nodes dramatically regressed
3	14-59-55 LS	45 WF	Hodgkin's disease		12,000 r	1/13/58		3	12	36+	Patient returned with involvement of cervical spine; tracheal compression
4	14-59-46 AM	3½ WM	Wilms's tumor with lung metastases		12,000 r	1/20/58	4/22/58	0	3	0	
5	14-67-92 GM	57 WM	Carcinoma of pancreas, islet cell		12,000 r 12,000 r	3/11/58 6/11/58		2	9	18+	Large epigastric mass decreased in size; recurred but did not respond as well with second course of treatment; died 1/29/59
6	11-75-80 JT	74 NM	Liposarcoma of scrotum		12,000 r	6/16/58		3	6	18+	At most recent follow-up doing well; no residual mass
7	14-33-91 SD	55 WM	Lymphosarcoma		1,200 r 1,200 r (incomplete)	11/14/58 11/17/58		1	2	2+	Only 2 treatments; considerable improvement in one month's time; died 1/13/59

* See footnote to Table VIII.

of the upper third of the esophagus. Thoracotomy on July 10, 1957 revealed a carcinoma which involved the esophagus from the thoracic inlet to the azygos vein. The mediastinal and paravertebral lymph nodes were involved. Although the primary lesion was considered nonresectable, because of atelectasis of the right middle lobe, a lobectomy was performed. Microscopic examination showed poorly differentiated squamous cell carcinoma of the esophagus.

The patient was referred for therapy, and it was elected to attempt palliation by grid therapy. The following factors were used: Barnes-Keleket telecobalt apparatus; half value layer 12 mm. Pb; field size with grid 13×13 cm.; 50 cm. skin source distance. A superior anterior midline chest portal was employed. A dose of 1,200 r was given daily for a total of 12,000 r (July 31, 1957, to August 13, 1957). During the follow-up roentgenographic examinations, the esophagus showed remarkable improvement with the previously irregular, stenotic segment becoming smooth and patent (Fig. 3, *A* and *B*). The patient was able to swallow food, but the over-all clinical picture was not considered good and he died on October 25, 1957 (P-1, T-3, PI-3).

CASE III. TH 14-43-93 WM 65. *Epidermoid Carcinoma of the Left Maxillary Sinus.* The patient presented with a vague history of several months of swelling over the left cheek plus a bleeding sore below the right eye. Both of these areas had grown rapidly. Physical examination revealed a 3 cm. circular ulcerated lesion over the right temple with a 1 cm. elevation. This lesion bled freely. Grossly, the face was asymmetric, with the left cheek protruding 2 cm. further than the right. Inside the mouth, the entire left superior alveolar ridge was replaced by a 3×6×2 cm. elevated, granular, friable, easily bleeding lesion. Sinus roentgenograms revealed that tumor tissue had filled the entire left antrum, eroded the medial wall into the left nasal cavity, destroyed the floor of the left orbit, and dissolved and pushed out the anterior wall of the antrum so that several teeth were lying loose in the soft tissue. To prevent fatal hemorrhage, the left external carotid artery was ligated. Biopsy revealed poorly differentiated squamous cell carcinoma of the left antrum.

The patient's condition was considered completely hopeless. He was accepted reluctantly in order to attempt palliation of bleeding, pain, and tumor size. The following factors were used: Keleket-Barnes telecobalt apparatus; half value layer 12 mm. Pb.; field size with grid 13×13 cm.; 50 cm. skin source distance; 1,200 r as measured in air through a port centered over the left antrum was given daily. A total dose of

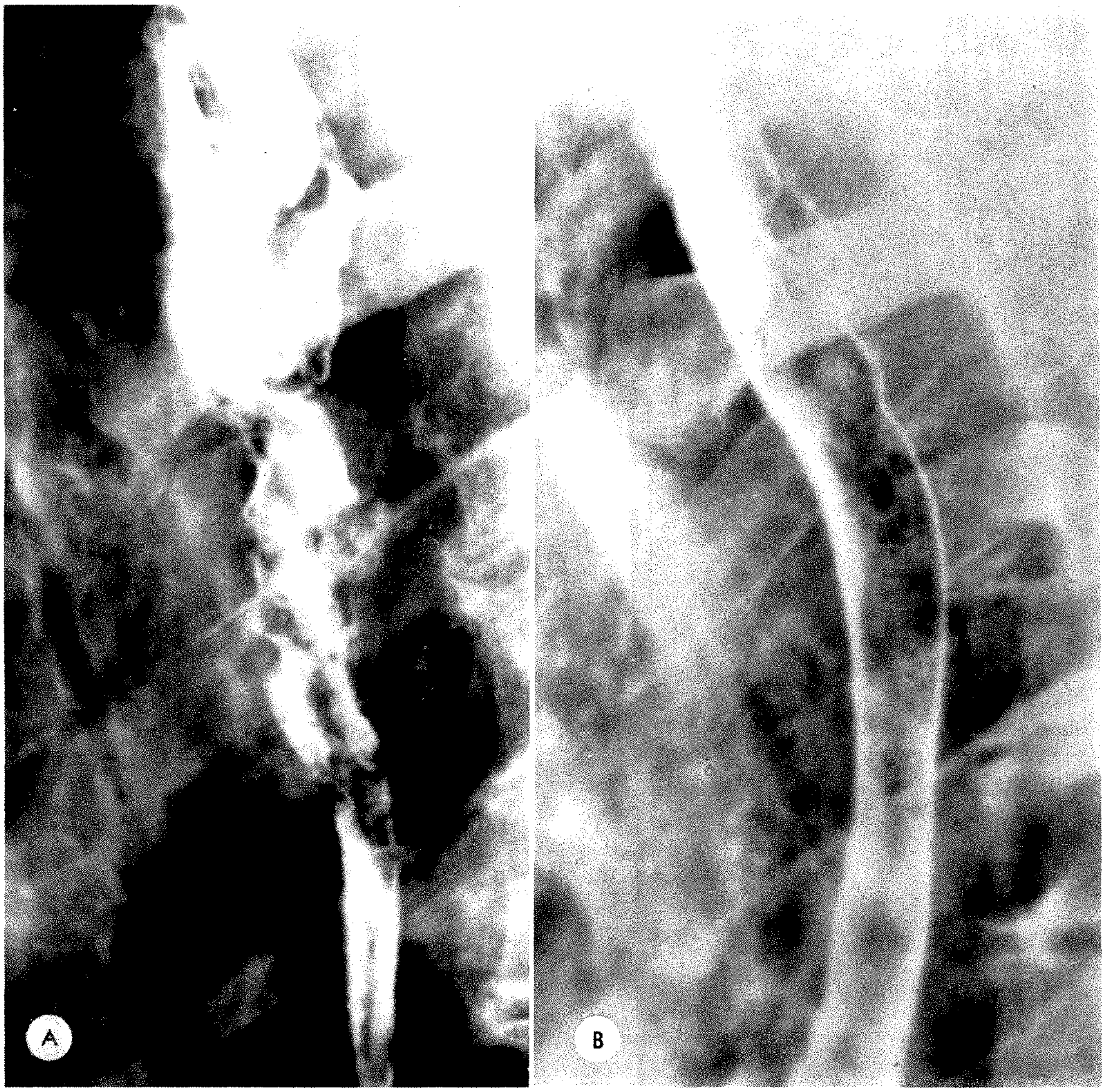

FIG. 3. Case II. Carcinoma of esophagus. (*A*) Pretreatment roentgenogram showing ragged tumor involving upper one-third of esophagus. (*B*) Post-treatment roentgenogram. Note smooth open lumen.

12,000 r was administered from December 10 to 24, 1957. Midway in the course of treatment, there was a noticeable decrease in the size of the cheek mass, and the patient had less pain and no bleeding.

Two months following completion of grid therapy, the patient returned with a symmetric face and no evidence of tumor involvement, by gross or by roentgenographic examination, in either the maxillary sinus or alveolar ridge.

Four months after treatment, the tumor was still not evident on the left side which had been treated. Roentgenograms demonstrated the left sinus to be essentially normal (Fig. 4, *A* and *B*). Physical examination and sinus roentgenograms revealed that the right antrum was now bulging with tumor. The patient suffered a cerebral vascular accident and, due to his inability to cooperate, the right side could not be treated. On May 7, 1958, the patient died in a nursing home (P-2, T-6, PI-12).

CASE IV. RA 13-48-62. *Adenocarcinoma of the Cervix—Stage IV*. This thirty-seven year old Negro housewife was referred to the hospital because of intermenstrual bleeding and lower abdominal cramps. About eight months before admission, the patient first noted intermen-

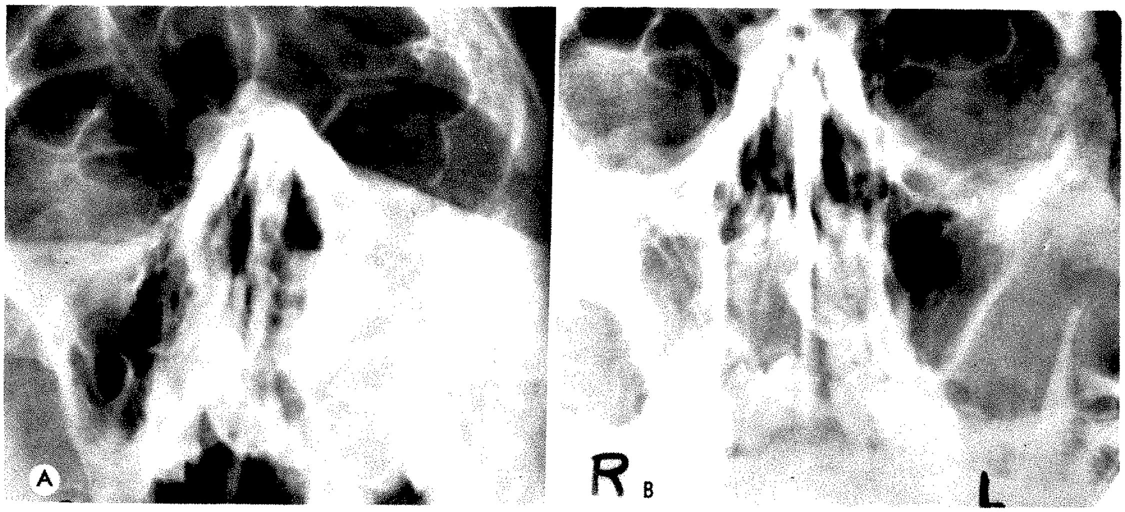

FIG. 4. Case III. Carcinoma of left maxillary sinus. (*A*) Roentgenogram showing pretreatment destruction. (*B*) Roentgenogram showing post-treatment improvement of left antrum.

strual spotting which was worse after intercourse. She had also developed a vaginal discharge. The patient said she had lost 20 pounds in weight and had increasing constipation.

Examination of the abdomen revealed a symmetric enlargement due to a hard, fixed, non-tender, fairly smooth mass arising out of the pelvis and extending to the umbilicus. Pelvic examination showed the cervix to be replaced by a friable, hard, necrotic mass of easily bleeding tissue. There was extension from the vesicovaginal septum to the introitus. The pelvis was filled with hard, fixed, non-tender masses and the adnexae were not identified. Rectal examination revealed marked narrowing and distortion $3\frac{1}{2}$ inches from the anus. Cystoscopic examination showed elevation and distortion of the bladder base, and sigmoidoscopic examination showed fixation and narrowing from a mass exerting extrinsic pressure on the right anterior wall of the rectum. The nonprotein nitrogen was 27 mg. per cent; hemoglobin was 6 gm. per cent and hematocrit 21.5. A biopsy revealed adenocarcinoma of the cervix.

The tumor conference considered surgery impossible and, although her condition was considered hopeless, the patient was accepted for grid radiation therapy. The following factors were used: Keleket-Barnes telecobalt unit, half value layer 12 mm. Pb; 50 cm. skin source distance; a 13×13 cm. grid was applied to the left and right anterior pelvis in two fields. Each side of the pelvis was treated on successive days to a total of 12,000 r in air delivered between the dates of May 27, 1957 and July 3, 1957. In subsequent visits the patient still complained of lower abdominal discomfort, but her bladder and bowel functioned normally. There was no bleeding. Pelvic examination revealed a large crater which replaced the cervix and was seen to be connected with the abdominal mass. The abdominal mass still filled the pelvis and lower abdomen to the umbilicus. The parametrium was frozen. Palliation was considered negligible. The patient died on September 23, 1957 at home (P-0, T-4, PI-0).

CASE V. WM 14-44-70. *Carcinoma of the Lung.* This patient was a fifty-seven year old white man who came to the clinic on December 13, 1957 complaining of a chronic cough productive of purulent sputum for twenty years but aggravated in the past six months. During the last two months he had developed a precordial pain and smothering spells which he associated with his cough. The pain radiated to the shoulders. Anorexia, dysphagia, and a weight loss of 15 pounds were also noted. In recent weeks there had been some blood flecks in the sputum. This patient had been a heavy smoker—almost two packs a day since he was eighteen years of age.

Physical examination revealed a thin, slightly dyspneic white man who appeared chronically ill. Distention of the neck veins and veins of the arm and chest was noted, as well as enlargement of the lymph nodes in the right supraclavicular region. The trachea was de-

viated to the left. A chest roentgenogram revealed a mass in the right upper mediastinum 7 cm. in diameter involving the right hilus and probably the superior vena cava. Bronchoscopic examination showed compression of the trachea from a mass on the right side. Biopsy revealed chronic inflammation but no tumor. A thoracotomy on January 9, 1958 disclosed a large slightly nodular mass extending from the right hilus to the right superior mediastinum. The mass displaced the trachea to the left and infiltrated the thoracic inlet. The surgeon did not consider the obvious tumor tissue resectable. Microscopic examination revealed necrotic debris, strands of fibrous tissue, and atypical cells.

The patient was referred for grid telecobalt therapy and the following factors were used: Keleket-Barnes telecobalt apparatus; half value layer 12 mm. Pb; 50 cm. skin source distance; a grid portal 13×13 cm. was applied to the right anterior chest. From January 16 to 29, 1958, 1,200 r per day was given to a total of 12,000 r as measured in air in the hole center. In subsequent follow-up visits, although the mass had decreased in size as seen roentgenographically, and the obstruction of the superior vena cava had regressed, the patient was still considered to have negligible palliation because of dyspnea. He died on April 9, 1959 at home. No autopsy was obtained (P-0, T-2, PI-0).

Case VI. AP 15-95-68. *Squamous Cell Carcinoma of the Hard Palate.* The patient was a fifty-nine year old Negro woman who complained of swelling in the left jaw and pain of approximately five months' duration. She had been referred by her family doctor with a diagnosis of possible pterygoid abscess of the left jaw. Her health had been fair until June, 1958 (about six months before admission), when she noted a pain and tooth ache in the left upper jaw that became progressively worse. She had intermittent attacks of chills and fever. On physical examination her temperature was noted to be 102.6°F.; her breath was foul; and she appeared acutely ill. There was marked swelling and tenderness in the left upper jaw with a palpable mass extending deep into the subcutaneous tissues in the roof of the mouth. The mass was 8 cm. in size and extended to the zygomatic arch. Massive edema was noted on the left side of the face from the temple to the submaxillary area. There was associated tenderness, redness and heat. Inside the mouth the one remaining molar tooth was tender and there was a necrotic and fluctuant mass over the posterior alveolar margin, both medially and laterally. Incision and drainage were done and necrotic purulent material was found in a large cavity. Microscopic sections revealed poorly differentiated squamous cell carcinoma of the hard palate.

The patient was accepted for grid palliative therapy. The following factors were used: Keleket-Barnes telecobalt unit; half value layer 12 mm. Pb; 50 cm. skin source distance; a 13×13 cm. grid field was directed to the anterior left side of the face. Doses of 1,200 r per day were given from December 1 to 12, 1958, for a total of 12,000 r in air in the hole center. On subsequent follow-up visits, there was no regression in the size of the tumor or alleviation of pain. In fact, both the pain and size of the tumor increased. Repeat sinus roentgenograms showed further left maxillary sinus involvement and bone destruction. The patient died on April 29, 1959 at home. No autopsy was obtained (P-0, T-1, PI-0+).

CONSTRUCTION OF THE GRID

The grid used on these patients was constructed from a block of lead 10×10 cm. in area and 5.4 cm. thick (slightly less than 5 half value layer for Co^{60} radiation). Twenty-five holes 10 mm. in diameter are arranged in a square with 5 holes on each side. The holes are focused by diverging them toward the patient. The distance between hole centers on the source side is 16.3 mm. and on the patient side 19.3 mm. The ratio of lead area to hole area on the source side is 2.4:1 and the ratio of lead area to hole area on the patient side is 3.7:1.

DATA PERTINENT TO DOSIMETRY

The projected grid area at 50 cm. skin source distance is 13×13 cm. The distance between projected hole centers at 50 cm. skin source distance is 27.4 mm. With an open field intensity (cone #15) considered to be 100 per cent, the radiation intensity in the hole center at 4 mm. depth of the phantom is 85.3 per cent. At a 4 mm. phantom depth, the intensity in the hole center drops to 50 per cent at a radius of about 7 mm. around the hole center. The

ratio of the area with less than 50 per cent of maximum intensity to the area with more than 50 per cent is 3.9:1. The intensity in the peripheral holes compared to the holes in the center of the field drops off 10 per cent. The radiation between two adjacent holes of the lead block is 13 per cent of that in the hole center. The radiation between four holes is only 7 per cent of that in the center of the hole. At 4 mm. phantom depth, the ratio of mean intensity under the lead to that of the maximum in the hole center is 1:10. The same ratio at 19 cm. phantom depth is 1:2.9. The ratio of the volume dose with grid to the volume dose of an open field equals 1:3.3.

Our source originally had 1,100 curies and now has approximately 650 curies. The intensity of the radiation on the skin in the center of the hole is approximately 60 r per minute, and the time of delivery of a surface dose of 1,000 r is approximately sixteen minutes.

A study was made of the intensity distribution of radiation from one of the holes of the grid in the center of the field. By means of film dosimetry[5,7] exposed at various depths of a phantom, a family of symmetric distribution curves was obtained.[6]

A study of these curves showed that with increasing depth each succeeding curve becomes flatter. The curve shows a discrete grid pattern at superficial levels which becomes more homogeneous at deeper levels.

It was clinically important to check whether, with repetitive treatments with the grid, it was possible to obtain a good grid pattern distribution in the body. Accordingly, a film was placed underneath a patient and the grid was placed in the treatment position. One exposure was made and this film was used as a standard. The patient was moved and the grid was repositioned ten different times with the dosimetry film adherent to the exit port. It may be noted that the registration of the grid pattern on ten different positionings was remarkably close to the grid pattern produced with one exposure (Fig. 5).

BIOLOGIC EXPERIMENTS WITH GRID IRRADIATION OF MICE[4]

We attempted to find out the biologic significance of the grid irradiation by using it to kill mice and then comparing that dose with the dose required using the homogeneous beam. The 50 per cent lethal dose in 30 days time (LD 50/30) was about 700 r and the LD 50/30 for grid radiation was 1,800 r. The ratio of the grid LD 50/30 to the homogeneous beam was 2.5:1.

Judging from this biologic end point, the clinical doses may well have been too small. In future clinical experimentation with apparatus with a high rhm, a higher total dosage should be investigated.

The grid used in animal experiments was considerably finer than the clinical one. The ratio of the homogeneous volume dose to that of the grid was 2:1. There is a real possibility that a biologic sparing factor exists in favor of the grid, since a given volume grid dose equal to the homogeneous volume dose exerts a lesser biologic effect as indexed by the LD 50. For local irradiation, the sparing ratio may favor the grid even more.

DISCUSSION

In this series of 87 cases of cancer, the disease was so advanced that under ordinary circumstances the radiotherapist would not have accepted the patient for treatment. Conventional therapy has some disadvantages. The duration of treatment is long compared to the short life expectancy. Frequently there is aggravation of pain and suffering due to local reaction. There is also generalized malaise due to massive destruction of tumor cells as well as diminished viability of normal tissues. Occasionally, with conventional therapy, a paradoxical cure is obtained—the tumor tissue is destroyed but the anatomic and physiologic integrity of a vital organ is disturbed sufficiently to cause death.

In telecobalt grid therapy, it has been possible to deliver a relatively large dose of radiation within a period of ten treatment days. Many of the patients experienced relief of pain and hemorrhage and showed

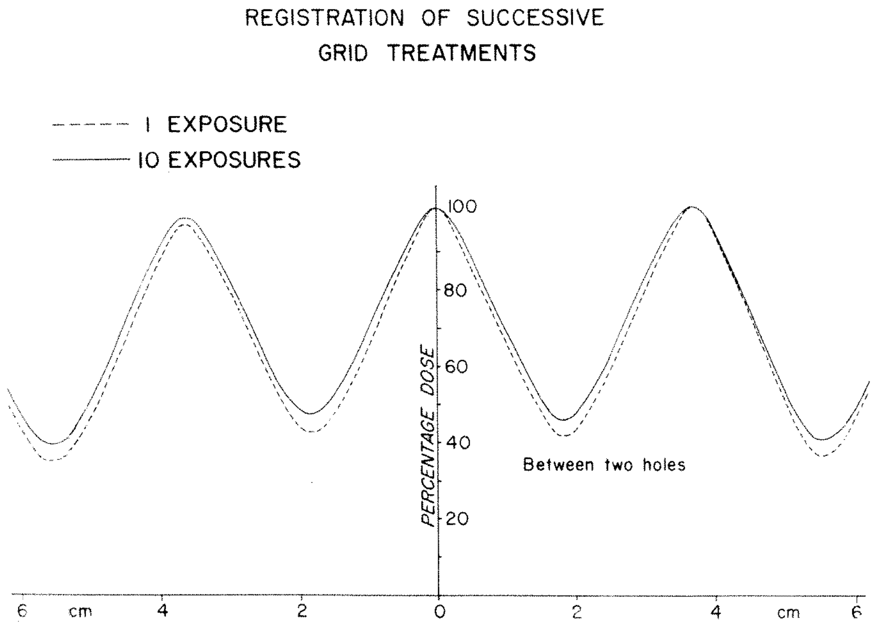

FIG. 5. A registration comparison of dose measurements during 1 exposure with those during 10 exposures by means of film dosimetry.

marked regression in tumor size. Some of the organs involved returned to a more normal function. This method of treatment contributed little or no discomfort to the patient during or after treatment. The advantages of this method have made it feasible to accept many more patients with advanced cancer. While it is probable that the longevity of the patient has not been improved to any great degree, the treatment has added considerably to his comfort.

The exact biologic mechanism of this mode of therapy is speculative. The nonhomogeneity of the grid radiation pattern may be analogous to a geometrically perfect radium implant (Fig. 6). It is well known that radium implants can give striking therapeutic results in the treatment of cancer.

The one feature that both the radium or cobalt implant and grid therapy have in common is a cyclical pattern of energy absorption in the tissue. Both methods have high gradients in the dose distribution.

It is rather remarkable that the measurement of the dose distribution in grid therapy is close to the calculated dose distribution of a needle implant. One calculation through the midplane of a needle implant yielded a ratio of approximately 1:5 when the area of more than 50 per cent of the maximal dose was compared with the area of less than 50 per cent of the maximal dose. The same ratio with grid therapy was approximately 1:4.

With grid therapy, the gradients are higher in the superficial structures and have a tendency to diminish in the deeper structures. The superficial tissues are thus spared to a greater degree than the deeper tissues. The grid pattern with telecobalt therapy is maintained at much greater depths in the tissue than with the conventional grid therapy. Preliminary data in animal experimentation indicate that there may be a biologic sparing factor which is in favor of the grid. It is not inconceivable that grid therapy may work by killing enough tumor cells to release sufficient antigens to elicit immune responses to cancer cells by adjacent normal cells and the immune mechanisms of the body. Pending biologic proof, it must be assumed that the grid telecobalt therapy increases the beneficial gradient between killing the

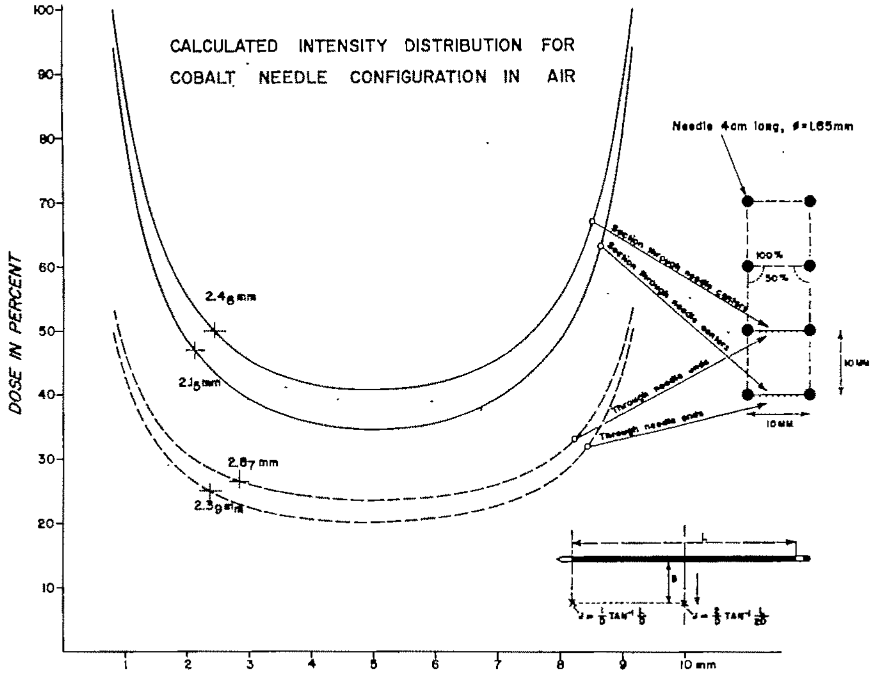

FIG. 6. An analogy can be drawn between radium needle implants and grid therapy. Note similarity of dose gradients of grid in Figure 5.

cancer cell and sparing the normal cell. It is agreed that some cancer cells do not receive much radiation and will remain viable. Even if neoplastic cells remain viable, the tumor bed and the humoral and cellular defense mechanisms may be so modified that the tumor becomes incapable of further growth and aggression.

SUMMARY

A series of 87 cases of advanced cancer was treated with focused telecobalt grid therapy. Fifty-one patients (59 per cent) experienced appreciable to striking palliation. No palliation was observed in 36 patients (41 per cent). The best palliation results were in patients with carcinoma of the bladder (78 per cent) and the least impressive in patients with carcinoma of the lung (36 per cent).

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MOVING-BEAM THERAPY WITH COBALT 60: ITS ADAPTABILITY TO THE LESION SHAPE TO BE TREATED*

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THE concept of moving-beam therapy, either as arc therapy or as rotation therapy, was first brought forward and partly explored as early as 1914, and accounts of this type of therapy have appeared in the literature from time to time (*e.g.*, Dessauer *et al.*,[3] 1937; Flax,[5] 1937; Hawley,[8] 1940; Munson,[11] 1946). The wider practical application of the method, however, has only a few years' history (O'Connor,[12] 1956; Fowler and Farmer,[6] 1957; Morrison *et al.*,[10] 1957; Farmer,[4] Fowler,[7] Chance,[2] Snelling and Stern[13], 1958). This developed, initially, against the background of roentgen therapy pursued with what we now regard as relatively low, conventional roentgen-ray energies, ranging from 200–250 kv. Its purpose was primarily to improve upon the tumor dose values, relative to skin dose, that can be obtained by multiple-beam techniques with this type of radiation, especially for such deeply seated and approximately centrally situated sites as the esophagus.

It happened that while the methods of moving-beam therapy and the associated techniques for dose computation were becoming a practical possibility, supervoltage apparatus, using either roentgen-ray generators or, more simply, highly active radioisotope sources, were also becoming more readily available. It was probably inevitable, therefore, that moving-beam supervoltage equipment soon came into production (*e.g.*, Braestrup *et al.*,[1] 1953) and this possibly without much inquiry as to whether the marriage between the movement of the beam and the beam itself was a marriage only of convenience, or of real additional therapeutic value.

There is a school of thought that considers the use of a moving-beam unnecessary for supervoltage therapy with beams of cobalt 60 gamma radiation or roentgen rays generated at 2 million volts or more. This school considers that with this radiation it is possible, by means of ordinary, but well planned multibeam techniques, to deliver completely adequate tumor doses to all sites without undue skin reaction. It sees little point, therefore, in adding the possible complexities and certain extra expense that moving-beam apparatus entails.

We must admit that, until we had personal experience with moving-beam supervoltage therapy, we also subscribed somewhat to this school of thought, but we must add that our reservations about the additional value it might have were also influenced by other considerations of a very different character.

It had seemed to us that, unless it is properly used for the most suitable cases, moving-beam therapy (expecially simple rotation therapy) carries with it the danger of attempting to fit the patient (or rather his disease) to the apparatus. This would be contrary to all the progressive development that has occurred in radiotherapeutic physics, which emphasizes the fitting of the apparatus (or rather its beam) to the patient. We were thus obliged to question whether a moving-beam apparatus would be applicable, as such, to more than a minority of the patients treated with it. Indeed, this question, either deliberately, or subconsciously raised, is possibly behind the attempt that is made on much moving-beam equipment to provide facilities also for fixed beam therapy.

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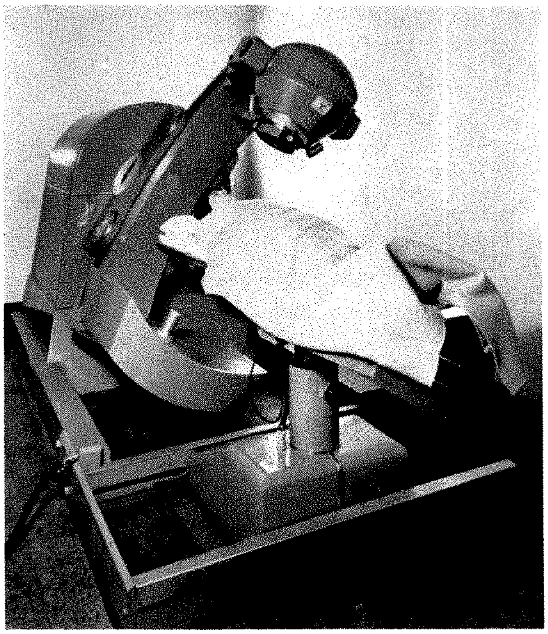

Fig. 1. The theratron rotating Co^{60} unit.

After nearly two years of experience with moving-beam supervoltage therapy with a cobalt 60 beam, we now realize that, provided sufficient attention is given to the physical planning of individual patients, it is possible to achieve a very wide, controlled range of dose-contour patterns such that very many patients may be treated by this form of therapy with distinct clinical advantage. It is the chief purpose of this paper to describe and illustrate a series of techniques for treating a variety of disease sites of different areas and shapes, in order to demonstrate this point.

THE MOVING-BEAM APPARATUS

The apparatus we have used is a theratron containing 1,750 c of cobalt 60 originally and made by Atomic Energy of Canada, Ltd. This apparatus (Fig. 1) readily permits rotation and arc therapy as well as other more complex procedures that we have not used as yet.

METHODS OF DOSE AND DOSE CONTOUR COMPUTATION

For the computation of dose and of the dose contours that represent the total dose distribution throughout the treated tissues, due to any particular rotation or arcing technique, we have found it preferable to apply the methods developed by Jones and his colleagues.[9] Originally, one of the disadvantages of rotation and arcing techniques had appeared to be the complexity of computation of complete dose distributions. These workers, however, have made it clear that with Co^{60} gamma radiation, or other equivalent radiation, many of the expected difficulties do not arise.

At first our computations were based upon our own measured dose contours expressed in the usual way with the maximum ionization (at 0.5 cm. below the treated surface) taken as 100 per cent. Atomic Energy of Canada, Ltd. has since produced carefully measured dose contours, in which the dose at the center of rotation is expressed as 100 per cent. We now prefer to use the latter since these permit more accurate interpolation.

LOCALIZATION OF DISEASE SITE AND AREA TO BE TREATED

For the determination and evaluation of a technique for treating any particular area at a given site, the first requirement is a suitable, accurate, anatomic contour of the patient, reproduced on paper, with the area to be treated precisely marked within the contour.

In practice the anatomic contour is obtained by means of one or other pieces of apparatus which need not be described here. The methods used for localization of the treated area within the contour depend upon the actual site of the disease and include palpation and direct measurement, direct radiography with or without radiopaque markers introduced at known positions, cystography with the patient in the treatment position, etc.

DECISION UPON AND EVALUATION OF TREATMENT TECHNIQUE

The treatment technique used is determined and evaluated with reference to the contour obtained as above. Initially, this

was a rather slow and tedious process because several possible techniques had sometimes to be examined before the most desirable one was found. However, with experience and the accumulation of data that may be used repeatedly, it is now possible to arrive at a satisfactory technique relatively quickly.

The complete dose-contour system for any chosen technique is determined by means of the methods already referred to (Jones *et al.*,[9] 1956) and the daily dose, treatment time, etc., are specified in the light of these contours. It is our aim in producing a suitable technique, to include the area to be treated as accurately as possible within the 80 per cent dose contour, where 100 per cent is the maximum dose delivered within the treated area.

PRACTICAL REALIZATION OF PLANNED TREATMENT TECHNIQUE

That all patients are treated lying down and that the beam may easily be rotated into any position make the accurate realization of a desired moving-beam technique simpler than is the case with ordinary fixed beam techniques. The essential requirement, of course, is that the center of rotation of the beam be correctly positioned within the patient.

At the time of the first treatment of a given patient, by means of a specially designed bridge that fits temporarily onto the treatment couch and over the patient and using the beam-defining and beam-exit light indicators, a number of surface markings are made on the skin which enable one to position the patient correctly on this and future occasions. The whole of this procedure is greatly facilitated by the motorized movements of the couch which enable the patient to be moved very easily and quickly in any desired direction.

SOME EXAMPLES OF VARIOUS TECHNIQUES

1. *Treatment of Carcinoma of Uvula by Full 360° Rotation.* The field used was 4 cm. wide (×8 cm. long) at the center of rotation. Figure 2 shows the dose distribution obtained with full 360° rotation. This is a typical distribution for full rotation—almost circular dose contours and a rapid fall of dose with distance from the center of rotation. In this and the following illustrations the area to be treated is delineated by the broken line.

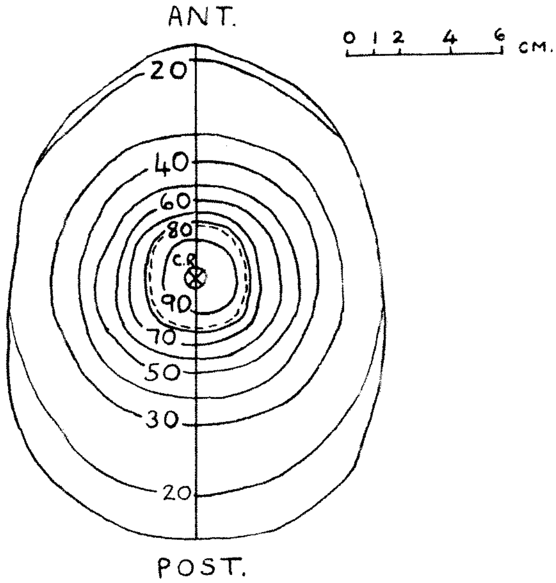

FIG. 2. Basic 360° rotation treatment of the uvula.

2. *Treatment of Carcinoma in the Nasopharynx Using One Rotation Center and Two Equal Arcs.* This case (Fig. 3) illustrates how the dose contours may be made oval in

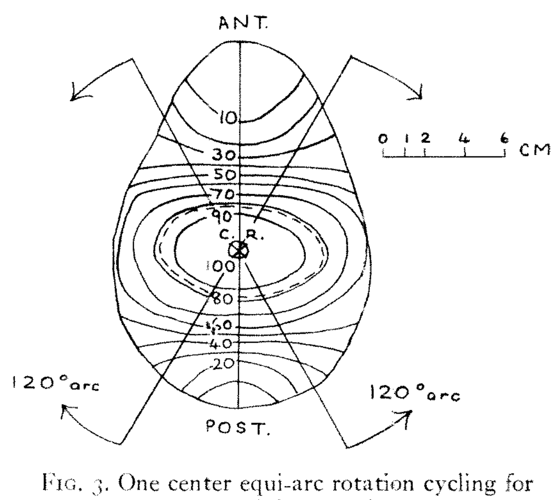

FIG. 3. One center equi-arc rotation cycling for treatment of the nasopharynx.

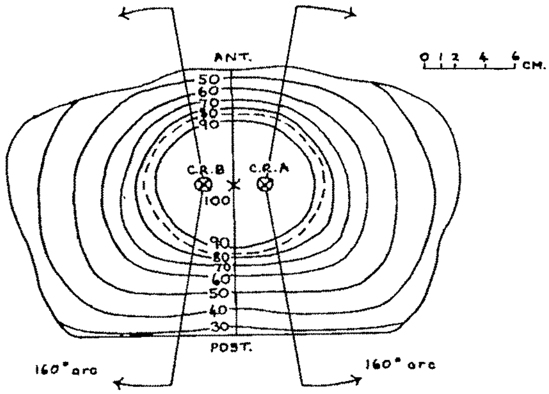

FIG. 4. Two center equi-arc rotation cycling for treatment of the bladder.

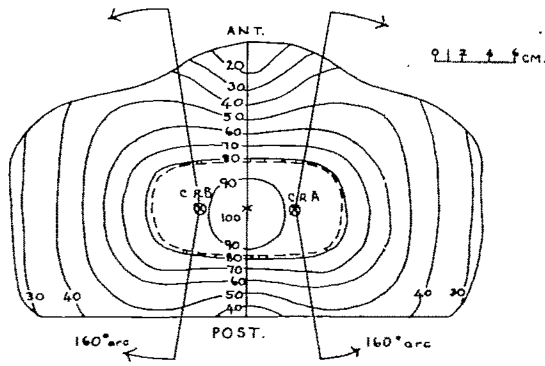

FIG. 5. Two center equi-arc rotation cycling for treatment of the cervix uteri.

shape for the treatment of a limited volume of that shape, lying within the head or neck. Two lateral arcs of rotation are used with one common center of arcing. Each arc is of 120°, the central anterior and posterior regions of 60°, each being omitted from the treatment. The dose distribution shown is for a field 6 cm. wide (and 8 cm. long) at the center of rotation.

3. *Treatment of Carcinoma of the Bladder and Carcinoma of the Cervix by Means of Two Equal Arcs about Two Different Centers.* This kind of technique is especially useful when a large and approximately oval area is to be treated within the pelvis.

Figure 4 illustrates its application to the treatment of the whole bladder, this customarily being the objective at Westminster Hospital in the radiation treatment of carcinoma of the bladder. The field size used in this case is 10 cm. wide (×12 cm. long) at the center of arcing. The fall-off of dose towards the rectum is fairly rapid and the bladder is covered very adequately.

Figure 5 shows the use of the same principle for treating carcinoma of the cervix so that tissue out to the pelvic wall is included in the (80 per cent dose level) treated area. The arcing centers are more widely separated than before in order that the required larger volume is encompassed satisfactorily. In this example, the field is 10 cm. wide (×15 cm. long) at the center of arcing.

This technique is being applied to a series of advanced cases as *the* method of treatment, no intracavitary radium therapy being used.

4. *Treatment of Extensive Carcinoma of Floor of the Mouth by Means of Two Unequal Arcs about Two Different Centers.* This case called for irradiation of an area of considerable magnitude and elongation which extended almost to the skin surface. It is of interest also because the latter feature would normally lead one to consider that little is to be gained by the use of moving beams.

Figure 6 shows the dose distribution actually obtained by the use of two different centers of arcing and two different

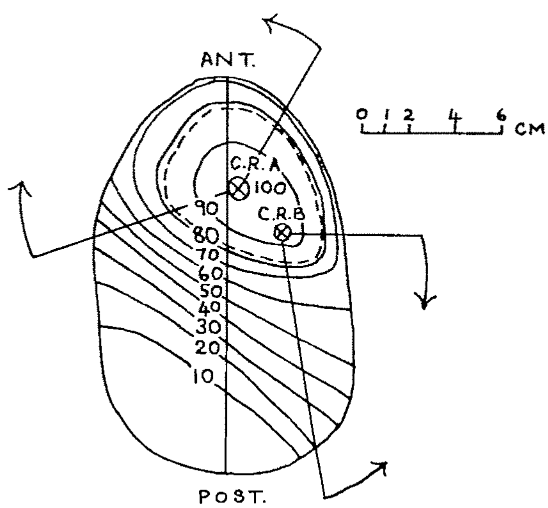

FIG. 6. Two center rotation cycling with two unequal arcs for treatment of an extensive area of the floor of mouth.

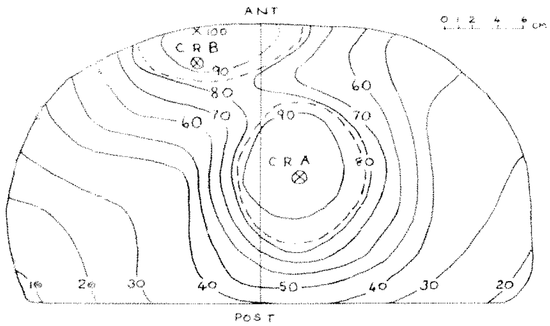

FIG. 7. Combined distribution for treatment of a recurrence in the vagina and a lymph node mass in the left groin (Figures 8 and 9 combined).

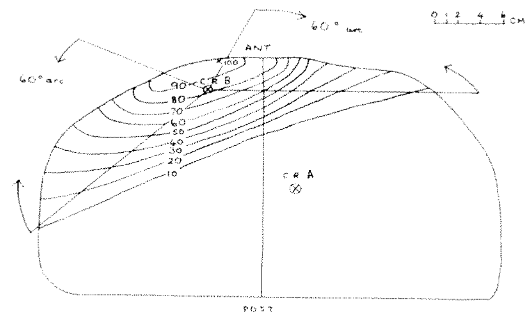

FIG. 9. One center equi-arc rotation cycling to treat the lymph node mass (see Fig. 7).

arcs. The field used was 6 cm. wide (×10 cm. long) at the arcing centers.

5. *An Attempt to Irradiate Two Separate Areas by Means of a Common Technique.* In this case of recurrent carcinoma of the vagina and a lymph node mass in the left groin, an attempt was made to devise a moving beam technique that would treat both these areas effectively.

The final dose distribution obtained is shown in Figure 7 where the two distinct zones of effective dose may be seen. This was achieved by what is really the summation of two separate techniques, each along the lines of those already described. Each of these uses two different arcs and one center of arcing and the dose distributions due to them separately are shown in Figures 8 and 9, in which the field sizes are 10 cm. in width (×15 cm. in length) and 6 cm. in width (×15 cm. in length), respectively, at the arcing centers.

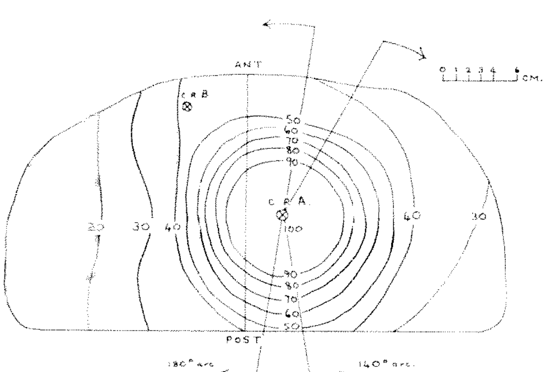

FIG. 8. One center rotation cycling with unequal arcs to treat the recurrence in the vagina (see Fig. 7).

GENERAL REMARKS

In all these techniques the emphasis has been upon the plane of rotation or arcing and the field used has been made sufficiently long to include the diseased tissue adequately in the direction perpendicular to this plane. Although we have not yet been able to pursue this aspect of the problem, it may be possible, by further elaboration of beam movement which the apparatus will in fact permit, to fit dose contours fairly closely to the disease in three dimensions.

SUMMARY

A series of moving beam techniques for treating a variety of disease sites of different areas and shapes, achieved by individual patient planning, is described. The very wide range of dose contour patterns which can be produced is arrived at by using multiple arcs and centers of rotation; thus a greater number of tumor sites may best be treated by a rotation technique than would first appear.

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We wish to acknowledge our indebtedness to Miss Nancy Legg, M.S.R.T., who carried out many of the computations necessary to determine the dose distributions we have shown.

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COBALT 60 TAGGED B_{12} AS A DIAGNOSTIC TOOL IN THE GENERAL ISOTOPE LABORATORY

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During the past seven years there have been many reports on the use of Co^{60} tagged B_{12} as a diagnostic tool.[2,3,5–8,10,12] It has been used by the gastroenterologist to evaluate intestinal tract absorption; the hematologist uses the study to evaluate hyperchromic anemias, and the neurologist and neurosurgeon use it when combined systemic disease is suspected. However, there have been no reports from a general isotope laboratory of its use in unselected cases. In presenting our material it is hoped that a clear-cut abnormal range can be identified. Also some of the pitfalls of the test will be pointed out for those planning to use it.

METHOD

All our studies were done by the urinary excretion method. The work of MacLean and Bloch[6] has shown this to be a valid technique. We have followed basically the Schilling procedure.[11] Our test meal contains 0.25 μg. of B_{12}, and this in turn contains 0.25 μc of Co^{60} radioactivity. Schilling originally used 2 μg. of B_{12} and 0.5 μc of Co^{60}.[11] Both of these test meals are in the physiologic range.[2,3,9] According to Glass and associates,[2,3] the absorption efficiency is best when the dose is under 2 μg. of vitamin B_{12}. The test meal was given only to patients fasting at least eight hours. No additional food was permitted until the 1,000 μg. flushing dose was given two hours later. Regular meals were then allowed. Barium does not alter the test.[1] All urine was collected over the next twenty-four hours and counted in 1,000 cc. aliquots and compared to a standard containing 20 per cent of the administered dose. Cobalt 58 B_{12} may have advantages but we have had no experience with it.[4]

MATERIAL

A total of 624 tests has been done. These patients have been referred to us by different services as shown in Figure 1. This is a reflection of interest and patient turnover on the respective services. It reflects a cross section of a general hospital.

RESULTS

The over-all results are shown in Figure 2. It will be noted that with the exception of the 2 per cent or less column, the results follow a uniform distribution curve. It logically follows that patients with an excretion rate of 2 per cent or under are abnormal. However, the 3 to 4 per cent group also deserves analysis. Of 36 patients in this latter group, 2 were felt to have pernicious anemia. No definite explanation or consistent diagnoses could be established in the others.

Of the 101 cases showing an excretion rate of 2 per cent or less, all were abnormal with the exceptions to be mentioned. Not all were checked with repeat studies and in-

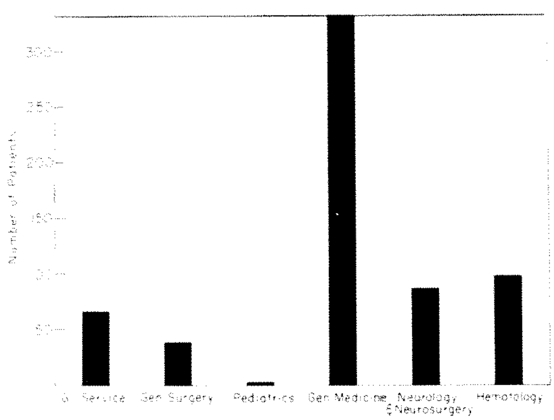

Fig. 1. Distribution of requests by various services Co^{60} B_{12} excretion test.

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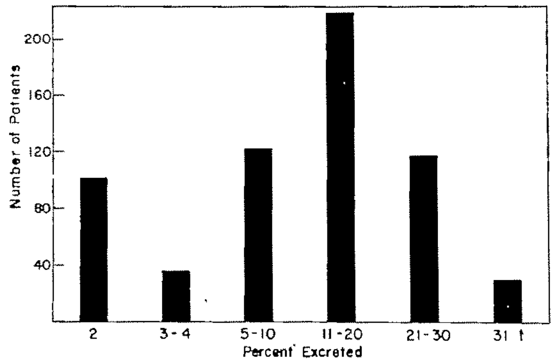

FIG. 2. Over-all results of Co^{60} B_{12} excretion test.

trinsic factor. One low test is sufficient for the diagnosis of pernicious anemia if this correlates with the clinical findings. Fifty-three of these cases were re-checked with intrinsic factor. The results are shown in Table I. Linitis plastica and total gastrectomy will produce results the same as pernicious anemia.[5] Three cases with questionable final diagnosis are listed in Table II. Cases 35 and 38 were listed in this group because we insist on the absence of free gastric hydrochloric acid for diagnosis of pernicious anemia. Case 22 may be pernicious anemia, but is so confusing we felt it should remain in this category.

The group subsequently proved normal also deserves comment. These cases occurred consecutively and aroused our interest. We felt that there existed some fault in the cobalt[60] tagged B_{12} supply. Repeat studies with a new shipment gave normal findings. Smith[18] has subsequently reported that radioactive B_{12} may be unstable.

Other sources of error include failure to give the flushing dose of nonradioactive B_{12} and an incomplete urine collection.[10] Food

TABLE I

RESULTS OF 53 CASES STUDIED WITH Co^{60} B_{12} AND INTRINSIC FACTOR

Pernicious Anemia	31
Malabsorption Syndrome	11
Linitis Plastica	2
Subsequently Proved Normal	6
Diagnosis Still Uncertain	3

TABLE II

CASES IN WHICH DIAGNOSIS WAS UNCERTAIN

Case 22	No anemia, no HCl, minor neurologic changes but also has diabetes and syphilis
Case 35	Neurologic consultation reported combined system disease but had free HCl
Case 38	Had free HCl, hyperchromic anemia and splenomegaly

or B_{12} ingestion within eight hours of the test will also alter the results.[1] If any of these factors are in doubt the test should be repeated.

SUMMARY

In the past there have been articles indicating that the excretion percentage of Co^{60} tagged B_{12} may be abnormal by as much as 13 per cent.[7] The distribution of results in our relatively large series would imply that only patients excreting 2 per cent or less are definitely abnormal. Those excreting 3 to 4 per cent are a border-line group which may be abnormal but usually is found to be normal, with some technical error occurring in the test. Certainly 5 per cent or above should be considered normal. The test is extremely valuable in the evaluation of patients with neurologic, hematologic and obscure gastrointestinal disease.

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INTRACAVITARY RADIOGOLD THERAPY*

A CRITICAL APPRAISAL OF ITS VALUE

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A COLLOIDAL solution of radioactive gold was successfully prepared and used in animal experiments by Hahn and co-workers[12] and employed in the treatment of malignant effusions in serous cavities in human patients by Muller[17,18] in 1947. Many reports have since appeared in the literature.[1,3,4,7,9,10,14,15,16,19,21,22,23,25] It is agreed that intracavitary radiogold therapy is not a curative treatment of cancer, but merely a palliative measure primarily for the reduction of fluid formation due to carcinomatosis, and that its usefulness is limited to carefully selected cases. Rather rigid criteria for the selection of patients have been advocated.[1,4,10,19,21] These, however, have seldom been heeded and various authors have lamented that their results could have been better had they selected their cases more strictly.[3,9,10,16,19,23,25] It would seem of considerable importance to know why this is so and how the therapeutic results may be affected. This information is sought in the following analysis of our series of 43 patients which is presented with other pertinent observations worthy of comment.

CLINICAL DATA

A total of 43 patients received intracavitary radiogold therapy: 17 for pleural effusion; 20 for ascites; and 6 for preventive treatment following discovery of peritoneal implants or spillage of cystic tumor content at laparotomy.

The sites and incidence of primary tumors in patients with pleural effusion are listed in Table I; those in patients with ascites in Table II. All of the 6 patients receiving preventive treatment had ovarian carcinomas.

The diagnosis in each patient was established by histologic examination of either the fluid or the tissue removed at operation or by biopsy or both. The importance of pathologic diagnosis has been emphasized by all workers because: (a) benign effusions may occur in cancer patients with associated cardiac, renal, hepatic, or nutritional diseases; and (b) benign effusions do not respond to radiogold treatment as a rule.[15,16,19]

TABLE I

PRIMARY TUMORS IN PATIENTS WITH PLEURAL EFFUSION

Site of Primary Tumor	No. of Patients
Lung	7
Breast	4
Ovary	3
Unknown	2
Pleura	1
Total	17

INDICATIONS AND CONTRAINDICATIONS

We believe that the criteria of Andrews *et al.*[2] are reasonable and realistic indications for intracavitary radiogold therapy. These may be summarized as follows: (1)

TABLE II

PRIMARY TUMORS IN PATIENTS WITH ASCITES

Site of Primary Tumor	No. of Patients
Ovary	7
Unknown	4
Appendix	3
Stomach	2
Uterus	2
Colon	1
Prostate	1
Total	20

* From The Department of Radiology, Baylor University College of Medicine and Jefferson Davis Hospital, Houston, Texas.

absence of symptoms due to neoplasm other than those related to effusion; (2) duration of effusion for several months before treatment; (3) absence of masses or lesions palpable or visible by roentgen-ray examination; and (4) absence of severe anemia and malnutrition.

Our experience indicates that these criteria have not been followed in many instances, with the predictable result of many failures.

SELECTION OF PATIENTS

Inasmuch as the Isotope Service sees only referred patients, the referring physicians of various clinical departments have the opportunity of preliminary selection of patients for radiogold treatment. In this respect, our experience indicates that, with a few exceptions, the referring physicians fall into two groups. There are those who refer all patients with effusion and those who refer none at all. It is our impression that the latter group may not know of or does not believe in this form of therapy. As a consequence of nonreferral, a number of patients suitable for radiogold therapy are denied the possible benefit without a consultation. The former group may honestly believe in the usefulness of radiogold therapy under *all* circumstances or, not infrequently, may just want to have everything possible done for their patients.

Of the referred patients, the final responsibility of selection rests with the isotope therapist. The decision with regard to indication for radiogold therapy should be based upon careful evaluation of the total picture of the patient: his disease, his symptomatology, and his prognosis. Good judgment depends upon absolute objectivity as well as sound experience. However, the isotope therapist may be pressed and tempted to give treatment even though the indication may not be clear in his better judgment. Treatment may be urged by the referring physician pleading for something to be done and arguing that nothing can be lost. Occasionally, the patient's family may express the desire for radiogold therapy. Consequently, some patients receive radiogold therapy when little or no palliation could be expected.

METHOD OF ADMINISTRATION AND DIAGNOSTIC SCAN

A number of methods and equipment for the administration of radiogold have been advocated.[6,8,11,13,24] We have adopted the simplest. The body cavity involved is tapped with a special 13 gauge trocar; as much fluid as possible is removed. A thin polyethylene tubing is threaded into the body cavity through the trocar, which is then withdrawn. By gravity displacement, the radiogold solution is flushed through the polyethylene tubing into the body cavity with a small volume of sterile normal saline solution.

Before the therapeutic dose of radiogold is delivered, a tracer amount (1–5 mc) may be given and a preliminary scintiscan is made after adequate distribution has been obtained. The polyethylene catheter is retained while the scan is being made.

This procedure is especially useful in cases where loculation is suspected. If the preliminary scan shows undesirable distribution or loculation, the therapeutic dose may be reduced or the treatment cancelled.

If the scan shows satisfactory distribution of the tracer dose (Fig. 1, *A* and *B*), the full amount of the therapeutic dose may then be given through the retained catheter. The puncture wound seldom requires suturing. A colloidin seal and a tight dressing are usually sufficient in preventing leakage.

DOSAGE AND TREATMENT SCHEDULE

The average single dose of radiogold given to our patients was 75 mc for pleural effusion and 150 mc for ascites.

A number of patients received more than one treatment. The reasons for multiple treatments are: (1) fractionation, (2) involvement of multiple cavities, and (3) retreatment. Our data are summarized in Table III. The number of cases is too small to warrant further discussion.

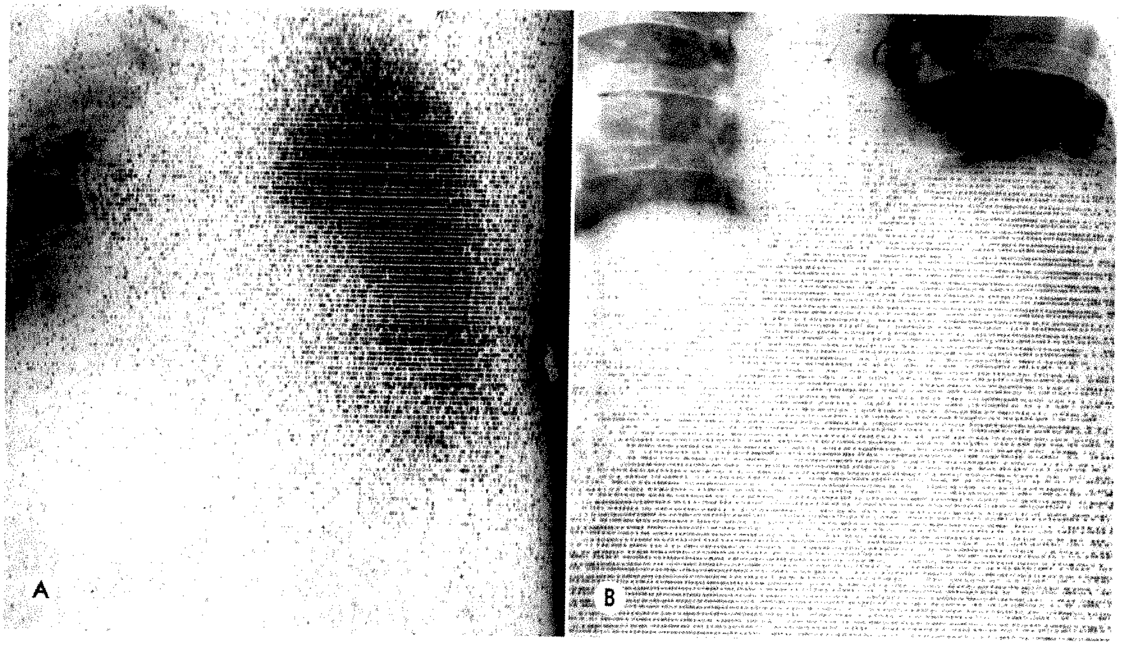

FIG. 1. Photoscintiscans of chest and abdomen following intracavitary radiogold injection. (*A*) Chest scan of a patient with inoperable mesothelioma and pleural effusion made after a tracer dose of radiogold showing satisfactory distribution. Note left cardiac border and mediastinal displacement. (*B*) Abdominal scan of a patient with ovarian carcinomatosis and ascites showing satisfactory distribution of radiogold. Note outline of liver.

RESULTS AND COMMENTS

It is recognized that the administration of 50–250 mc of radioactive gold into a pleural or peritoneal cavity with malignant effusion has no curative effect on the malignant disease. Its only palliative effect is the reduction or stoppage of fluid formation, and this is the sole objective of the treatment.

On this score, the results of therapy are rated as excellent, equivocal, or nil. Excellent result denotes marked reduction of fluid formation requiring, at most, one or no more tapping in patients surviving three months or longer. Equivocal result denotes patients surviving less than two to three months with only dubious change in the rate of fluid accumulation. Nil result denotes patients surviving less than one month with little or no change in the rate of fluid formation. Table IV shows the results in our cases. The figures are in accord with those reported in the literature. The high percentage of patients receiving doubtful or no benefit is largely attributable to the brevity of survival. Thus 9 of 17 patients with pleural effusion and 10 of 20 patients with ascites were dead within two months after the administration of radiogold (Table V). These early deaths were attributable primarily to the advanced stage of cancer. The clinical picture of cachexia, anemia, pain, etc., should have contraindicated radiogold therapy. If these cases had been excluded by proper selection, the figures would have shown 4 of 8 patients with pleural effusion and 6 of 10 patients with ascites demonstrating excellent response to radiogold treatment.

Further scrutiny of our data reveals that almost all of the patients with effusion of acute onset, short duration and rapid reaccumulation were dead within three weeks after the radiogold injection (Table VI). The uselessness of giving treatment to these patients at all is brought sharply into focus.

The data on the presence or absence of

Table III

SUMMARY OF MULTIPLE INTRACAVITARY INJECTIONS OF Au^{198}

Reason for Multiple Treatment	Case No.	Primary Tumor Site	Effusion	Dose and Schedule					Results
				1 (mc)	2 (mc)	3 (mc)	Total (mc)	Interval	
Fractionation	1	Ovary	Ascites	74	50	50	174	Weekly	Excellent
	2	Ovary	Ascites	50	50	74	174	Weekly	Nil
	1	Ovary	Pleural	34	94	60	188	Weekly	Excellent
Multiple Effusion	1	Ovary	Ascites	74	50	50	174	Weekly	Excellent
			Pleural	34	94	60	188	Weekly	Excellent
	3	Ovary	Pleural (right)	50	50	50	150	2 weeks	Excellent
			Pleural (left)	50			50	2 months	Excellent
Repeated Treatment	4	Ovary	Ascites	60	78		138	6 months	Excellent
	5	Ovary	Ascites	100	150		250	4 months	Excellent
	6	Stomach	Ascites	100	150		250	9 months	Excellent
	7	Appendix	Ascites	70	78	100	248	5 months 6 months	Nil
	8	Unknown	Ascites	40	70		110	1 month	Nil
	9	Breast	Pleural	50	60		110	30 months	Excellent
	10	Breast	Pleural	50	47		97	1 month	Nil
	11	Lung	Pleural	43	30	17	90	2 months 1 month	Nil
	12	Lung	Pleural	75	95		170	12 months	Excellent
	13	Pleura	Pleural	90	93	75	258	4 months 10 months	Equivocal
	14	Unknown	Pleural	75	75		150	1 month	Nil

demonstrable tumor mass in the peritoneal cavity in 20 patients with ascites are summarized in Table VII. Seven of 10 patients with demonstrable mass were dead within 2 months while 4 lived 3–12 months. Of 9 patients without demonstrable mass, 3 died within 2 months; 3 survived 13–16 months; and 3 are still living without ascites after radiogold therapy.

Of the 17 patients who have died of peritoneal carcinomatosis, 4 had received radium and/or roentgen-ray irradiation of the pelvis and 13 had not. Of the untreated group, 10 were dead within 2 months, while all 4 of the treated group lived considerably longer (Table VIII). It is interesting to note that the radiotherapists wisely withheld radiation therapy from the 13 patients because of the gravity of their condition.

While 4 cases is too small a number to warrant any conclusion, it would appear that radiotherapy may have retarded the growth of the primary tumor and contributed to the longer survival of the 4 treated patients;[4,10] and the prolonged survival provided a chance for radiogold treatment to be worthwhile. Muller's[17] superior results seem attributable to combined

Table IV

SUMMARY OF RESULTS OF Au^{198} THERAPY

Results	Pleural Effusion		Ascites	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Nil	6	35	10	50
Equivocal	7	41	4	20
Excellent	4	24	6	30

TABLE V

CORRELATION BETWEEN SURVIVAL TIME AND RESULTS OF INTRACAVITARY Au^{198} THERAPY

Survival Time (mo.)	Results		
	Excellent	Equivocal	Nil
17 Patients with Pleural Effusion			
2 or less	0	3	6
3–6	0	3	0
6 or more	4	1	0
20 Patients with Ascites			
2 or less	0	0	10
3–6	1	2	0
6 or more	5	2	0

therapy in a great majority of his patients.

The data on the 6 patients who received preventive radiogold treatment for peritoneal implants or spillage of ovarian tumor are summarized in Table IX. We entertain the same hopes as for the preceding group but feel, like most authors, that the results are difficult to evaluate.

DISCUSSION

When our results are examined, it becomes clear that intracavitary radiogold therapy has been used in many patients in whom its indication was doubtful or negative.

TABLE VI

SUMMARY OF PATIENTS WITH ACUTE EFFUSIONS

Primary Tumor Site	Duration of Effusion (wk.)	Tapping Interval (da.)	Survival Time after Au^{198} (da.)
5 Patients with Pleural Effusion			
Pancreas	1	1– 2	11
Lung	9	3– 4	106
Lung	4	7–10	20
Ovary	1	1– 2	20
Unknown	3	3– 4	4
4 Patients with Ascites			
Ovary	3	1– 2	11
Uterus	2	3– 4	10
Prostate	6	7–10	20
Unknown	3	2– 3	2

TABLE VII

SURVIVAL TIME OF PATIENTS WITH ASCITES WITH OR WITHOUT DEMONSTRABLE MASS

Survival Time (mo.)	Demonstrable Mass	
	Present	Absent
2 or less	7	3
3–12	4	0
13–16	0	3
Still alive	0	3

It is apparent that there must be a reasonable life expectancy of three months or longer for radiogold therapy to be of any real palliative value to the patient, for it may take several weeks for the therapeutic effect to be realized.[4,16]

Rapid accumulation of fluid requiring thoracentesis or paracentesis every ten days or less is, in our experience, a very grave sign of relentless progress of the underlying malignancy. Radiogold treatment in such cases is useless. These observations are in agreement with those of Andrews *et al.*[3]

The presence or absence of a demonstrable mass as a criterion against or for radiogold therapy seems less firmly established by our data. Here again, the life expectancy and general condition of the patient are more important factors than tumor mass *per se*. The patient with or without demonstrable mass should, therefore, be individually evaluated with regard to the suitability of radiogold therapy on the basis of other clinical findings.

TABLE VIII

SURVIVAL TIME OF PATIENTS WITH ASCITES WITH OR WITHOUT RADIOTHERAPY TO PELVIS

Survival Time (mo.)	Pelvic Radiotherapy	
	Yes	No
Less than 2	0	10
Up to 11	0	3
Up to 17	4	0

Table IX

SUMMARY OF CASES RECEIVING PREVENTIVE INTRAPERITONEAL Au^{198} THERAPY

Age	Primary Tumor Site	Reason for Treatment	Dose of Au^{198} (mc)	Follow-Up		
				Year	Status	Ascites
66	Ovary	Peritoneal implants	75	5	Living	0
48	Ovary	Peritoneal implants	43	2	Dead	0
37	Ovary	Peritoneal implants and spillage	100	1	Living	0
44	Ovary	Peritoneal implants	110	$\frac{1}{4}$	Dead	0
35	Ovary	Rupture of papillary cyst (adenocarcinoma)	70	2	Living	0
49	Ovary	? Spillage on removal of cyst (adenocarcinoma)	60	1	Living	0

The conditions governing palliation, in so far as radiation therapy is concerned, have been discussed by Paterson.[20] Two of the points he made are very pertinent here: (1) there must be reasonable expectation of relief; and (2) beyond a certain stage of decline, no palliation is possible. He wrote, "In the moderately advanced stages of disease, we can still do much to ease distress, but later when the patient has really begun to go downhill, is already febrile or cachectic and looks 'ill,' treatment is not a kindness and may even help to precipitate the end." With this view the laity concurs.[5]

It may also be mentioned that intracavitary radiogold treatment is an expensive procedure, averaging about $250.00 or more (Table x) per application.

SUMMARY AND CONCLUSIONS

1. Seventeen patients with pleural effusion, 20 patients with ascites and 6 patients with peritoneal implants received radiogold intracavitary therapy.

Table X

EXPENSE OF Au^{198} THERAPY

Average dose of Au^{198} (100 mc)	$ 50.00
Average stay in hospital (5 days)	100.00
Professional fee	$ 50.00–100.00
Miscellaneous expenses	50.00
Total	$250.00–$300.00

2. Nine of 17 patients with pleural effusion and 10 of 20 patients with ascites were dead within two months of treatment. In retrospect, these patients could not be expected to benefit from the radiogold therapy, the indication was doubtful or negative and the treatment results unsatisfactory.

3. Excluding the early deaths, the results of radiogold therapy were excellent in 4 of 8 patients with pleural effusion and 6 of 10 patients with ascites.

4. The factors and circumstances leading to unsatisfactory results are discussed. The importance of strict adherence to certain criteria for the selection of patients is emphasized.

5. Rapid accumulation and short duration of fluid formation were grave signs of relentless progress of the disease. They were observed in 5 patients with pleural effusions and 4 patients with ascites, all except 1 were dead within twenty days of radiogold treatment.

6. The presence or absence of mass *per se* is not a reliable criterion for the selection of patients.

7. It is the task of the isotope therapist to evaluate the total picture of the patient as a basis for his decision to give or to withhold treatment.

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THE DIAGNOSTIC AND PROGNOSTIC VALUE OF ORAL SMEARS IN THE RADIOTHERAPY OF CARCINOMA OF THE ORAL CAVITY AND OROPHARYNX

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The radiosensitivity of benign and malignant cells from carcinomas of the cervix uteri has been evaluated in tissue sections,[3,13] and in vaginal or cervical smears.[4–6] There has been a paucity of reports concerning similar studies of oral carcinomas, although Hall and Friedman[7] found that valuable prognostic information could be obtained by a single biopsy during the second week of irradiation of carcinomas involving the oral cavity and oropharynx. The cytologic effects of radiation on benign and malignant cells in oral smears have been described, and preliminary prognostic implications postulated on the basis of observations on a small series of patients.[9–12] This report concerns the evaluation of the diagnostic and prognostic significance of oral smears in a larger series of patients who received external irradiation for carcinomas of the oral cavity or oropharynx.

MATERIAL AND METHODS

Direct smears were obtained from the surfaces of 55 oral carcinomas (tongue, gingiva, floor of the mouth, anterior tonsillar pillar, retromolar area, and hard palate) prior to, during, and after irradiation. Companion smears were taken from the adjacent uninvolved mucosa within the field of irradiation. The smears were taken with small wooden spatulas, since metallic instruments either slipped over the mucosa without removing sufficient material, or produced bleeding if pressure was increased. Cotton-tipped applicators were found to be the least desirable, since the secretions were absorbed into the cotton. The smears were fixed immediately in ether-alcohol and stained according to the standard Papanicolaou technique.[8] In most instances the examinations were done daily or tri-weekly during treatment and monthly following completion of radiotherapy. The following studies were made:

1. *Radiation changes in benign squamous cells.* A minimum of 100 benign squamous cells was examined in each smear, and percentage determinations of the following cytologic features of radiation change were made: (a) enlargement of cell diameter above 75 μ; (b) enlargment of diameter of the nucleus above 14 μ; (c) vacuolization of cytoplasm; and (d) multinucleation.

2. *Radiation changes in malignant cells.* (a) Maturation of cells. This was determined by two indices of maturation; the nucleocytoplasmic ratio and the degree of cornification. The former was determined by separating the malignant cells into well-differentiated and poorly differentiated cells on the basis of their relative cell and nuclear diameters. If the diameter of the nucleus exceeded one-half that of the cell, the cell was classified as poorly differentiated; less than one-half, well-differentiated. The percentages of cornified and noncornified cells were readily determined, since the cytoplasm of the former stains intensely red or orange with the Papanicolaou stain, while the cytoplasm of the noncornified cells is cyanophilic. (b) Retrogressive changes. The percentages of Caspersson's type A and type B cells were determined.[2] About one-half of the patients

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had smears which were too hypocellular to make accurate determinations of the nucleoprotein patterns. (c) Ultraviolet microscopic studies of nucleic acids. The smears of 11 patients were stained with acridine-orange and examined with the ultraviolet microscope, using blue-violet light according to the technique of von Bertalanffy and his associates.[1] The same smears were decolorized and then restained by the routine Papanicolaou technique.

3. *Exfoliation of malignant cells.* The number of malignant cells per 100 benign squamous cells was determined.

4. *Conversion of positive to negative smears.* The date of the last positive smear during or following treatment was recorded. Emphasis was placed on the presence or absence of malignant cells at the end of treatment, during the immediate post-treatment phase (one to three months), and at the time of follow-up visits.

5. *Detection of recurrent neoplasm.*

RESULTS AND DISCUSSION

RADIATION CHANGES IN BENIGN SQUAMOUS CELLS

Although cell or nuclear enlargement, and cytoplasmic vacuolization or multinucleation are not pathognomonic of radiation effect, the quantitative transformations during treatment were striking.[9,10] Enlargement of the cells was the earliest, most prominent, and most consistent alteration. Cells which exceeded 75 μ in diameter were infrequent in pretreatment smears, while during therapy a majority of the cells showed some enlargement, often several times their pretreatment size, 35–50 μ. Increase in nuclear size was less frequent, probably because of the large number of superficial cornified cells with nonreacting pyknotic nuclei. Multinucleation appeared later, and the multinucleated cells rarely had more than two nuclei, in contrast to multinucleated malignant cells which often had many nuclei. Vacuolization of cytoplasm varied qualitatively and quantitatively from case to case more than any of the other changes and showed less constant sequential patterns in individual cases.

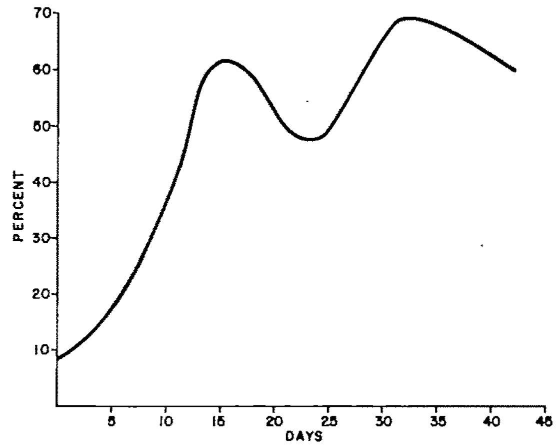

Fig. 1. Median percentage values of radiation change in benign squamous cells during treatment (55 patients).

Cytoplasmic inclusions of bacteria, leukocytes, and granules exhibited no correlation with duration of treatment, or with any of the above alterations, for which reason they were not included in the results.

Recognizable cytologic changes were usually distinct by the fifth to seventh day, and these observations were supported by quantitative analyses (Fig. 1). There were considerable differences in the cytologic responses in different patients, but the chronologic patterns in individual cases were remarkably uniform, supporting the validity of the daily counts. Most patients exhibited a diphasic pattern, there being a median peak at the end of the second week of treatment, and a slightly higher second peak between the thirtieth and thirty-fifth days. A smaller number of patients had patterns with a gradual step-like increase. The depression between the two peaks of maximum response in the diphasic curves may represent persistence of unresponsive cells following removal of more radiosensitive cells, a temporary phase of cellular insensitivity, an interval between two different modes of physical or chemical action, or a pause between the direct and indirect effects of radiation.[10]

Clinical manifestations of radiation effect, such as "mucositis" or membrane formation, were seen between the time of onset of cytologic radiation change and the point of maximum development of these alterations, while tumor regression was usually observed at the peak of cytologic change.

No constant correlation could be demonstrated between the radiation changes in benign cells and the exfoliation or rate of disappearance of the malignant cells, the maturation or nucleoprotein patterns of the malignant cells, or the development of radionecrosis.

Preliminary observations[9,10] had suggested a direct relationship between the radiation response in the benign cells and the radiotherapeutic control of the primary neoplasm. The present studies, with a larger number of patients and longer follow-up studies, have demonstrated less convincing correlation. The median cytologic changes were only slightly greater in patients whose primary neoplasms were controlled, and, although the data may show valid general statistical differences, they are not sufficiently precise to permit practical prognostication in individual patients, especially in comparison with the correlation between the size of the primary tumor and its therapeutic control (Table I). However, it was observed that the smears from each of the 4 patients who had uncontrolled *small* primary neoplasms (diameter of 2.5 cm. or less) exhibited poor cytologic radiation response, while the few patients without recurrence of large neoplasms at the end of twelve months or more showed vigorous cytologic responses.

TABLE I

RELATIONSHIP BETWEEN THE SIZE OF NEOPLASMS OF THE MOUTH OR OROPHARYNX AND PROGNOSIS

Clinical Status	Small (2.5 cm. or less in diameter)	Medium (2.5–3.5 cm. in diameter)	Large (over 3.5 cm. in diameter)
Total patients	19	7	25
Well	13	3	4
Residual neoplasm	4	1	16
Metastases	3	4	12
Dead	2	2	12

The characteristic "SR" cells described by Graham[4] in patients who had favorable radiotherapeutic results were rarely encountered, probably because such cells come from deep layers of the stratified squamous epithelium, and oral smears failed to disclose cells from these layers.

RADIATION CHANGES IN MALIGNANT CELLS

The radiation changes of the type described in benign cells were also demonstrated in malignant cells[12] but were more difficult to assess quantitatively because of the smaller number of cells and the frequent presence of similar alterations in non-irradiated cells. Attempts to measure these characteristics, therefore, were abandoned early in the study, and effort was directed instead to measuring the effects on maturation or differentiation of the tumors, and on Caspersson's criteria of variability.

Maturation, as determined by the nucleo-cytoplasmic and the cornification indices, was striking in only a few cases and showed no statistically valid correlation with clinical observations.

Caspersson and Santesson,[2] using ultraviolet spectrophotometric observations, found that the neoplastic cells in the growing and infiltrating, or perivascular portions of epithelial cancers were characterized by nuclei with abundant desoxyribonucleic acid (and chromatin). These were designated as type A cells in contrast to the type B cells which were found in the central, less viable areas of the neoplasm. The latter cells were regarded as prenecrotic, or at least less viable cells, and had nuclei which were larger, relatively poor in DNA, and rich in nucleolar ribonucleic acid (RNA). A preliminary study of 21 patients with oral carcinoma strongly suggested that these nucleoprotein patterns could be utilized to measure radiation ef-

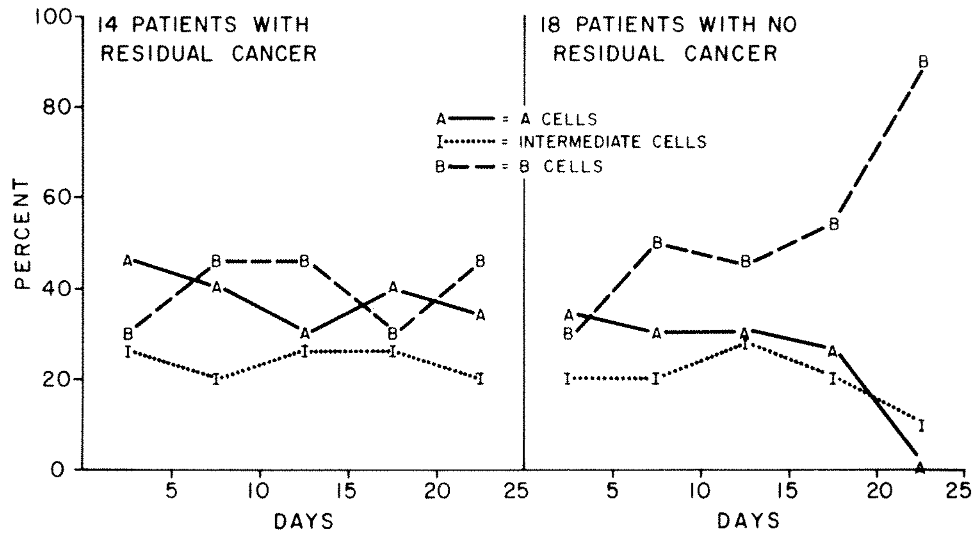

FIG. 2. Median percentages of Caspersson's type A and type B cells during irradiation.

fect in smears stained by the routine Papanicolaou method, and that there was a good correlation between the conversion of type A to type B cells and the results of radiation.[11] This line of endeavor has been amplified to include 11 additional cases, to investigate the additional follow-up of the original 21 cases, and to study the smears from another group of 11 oral cancers by ultraviolet microscopy using the fluorochrome, acridine-orange.

The findings of the current studies support our initial observations, namely, that the conversion from type A to type B cells is a good prognostic sign. As indicated in Figure 2, the median percentages of type A cells decreased only slightly in 14 patients who had residual carcinoma, while there was a pronounced decrease of type A cells and a proportionate increase in type B cells in the 18 patients with no clinical evidence of residual neoplasm. The contrast became most marked between the fifteenth and twenty-fifth days, although in some instances the critical measurements had to be made prior to this time because of the sparsity of malignant cells by the fifteenth day of treatment. In addition, the patients with good clinical radiation effect originally had fewer type A cells.

Unfortunately, these determinations were not possible in almost 50 per cent of the patients because of the lack of sufficient exfoliation. This information could probably be determined histologically by a single biopsy between the fifteenth and twenty-fifth days.

ULTRAVIOLET MICROSCOPIC STUDIES OF NUCLEIC ACIDS

von Bertalanffy and associates[1] demonstrated the specificity of DNA and RNA staining by acridine-orange with ultraviolet or blue-violet microscopy. In the usual maturation of benign or malignant squamous cells, there is a gradual decrease in cytoplasmic RNA and relatively less diminution in nuclear DNA. Irradiated cells, in contrast, showed more rapid reduction in the nuclear fluorescence, which changed from brilliant yellow to dull olive-green, while the cytoplasm remained bright orange until later in the treatment.

It was noted that even in the pretreatment smears a variable number of malignant squamous cells showed minimal fluorescence. These poorly-fluorescing cells were usually well-differentiated, cornified cells or markedly degenerated cells, which differed from the typical type B cells of Caspersson by the absence of demonstrable nucleoli. There was a gradual increase in these poorly-fluorescing cells during treat-

ment, and, in general, the observations corresponded to the changes in the nucleoprotein patterns of the nuclei noted in smears stained by the Papanicolaou technique.

The examination of nucleoli was facilitated by the acridine-orange technique, since the nucleoli could be distinctly visualized despite the high chromatin content of the malignant nuclei, whereas in the Papanicolaou stained control smears the nucleoli frequently were completely obscured by the nuclear hyperchromasia. The ultraviolet studies demonstrated relatively little change in the size or number of nucleoli during irradiation until the cells reached advanced stages of degeneration or maturation when the fluorescence of the nucleoli faded with that of the other cellular components. It was frequently observed that the nucleolar RNA was the last nucleic acid constituent to fade in fluorescence.

It is worthy of re-emphasis that the "active-appearing" malignant squamous cells, which have diffuse nuclear hyperchromasia and no apparent nucleoli when examined by the standard staining techniques and ordinary light microscopy, do have large and frequently multiple nucleoli, and the apparent increase in nucleolar size reported to occur during irradiation is due chiefly to the unmasking of the nucleoli by the decrease in chromatin density.

EXFOLIATION OF MALIGNANT CELLS

The propensity for desquamation was evaluated by counting the number of malignant cells in relation to the number of benign squamous cells. The smears from over one-half of the patients exhibited abundant cancer cells during the early phase of treatment, with malignant cells comprising 25 per cent or more of the epithelial cells. Twenty-five per cent of the patients consistently had such sparsity of malignant cells that the smears had to be searched diligently to detect any, while the remaining 25 per cent had smears which contained from 5 to 25 per cent malignant cells. Although there were minor variations in the malignant cell populations from day to day in individual patients, the percentage of malignant cells was remarkably constant and showed a definite sequential pattern in most cases. This attribute has been designated by us as one of exfoliation, for, although the smears represented direct scrapings, the fundamental property is still one of cohesiveness. The median values are illustrated in Figure 3.

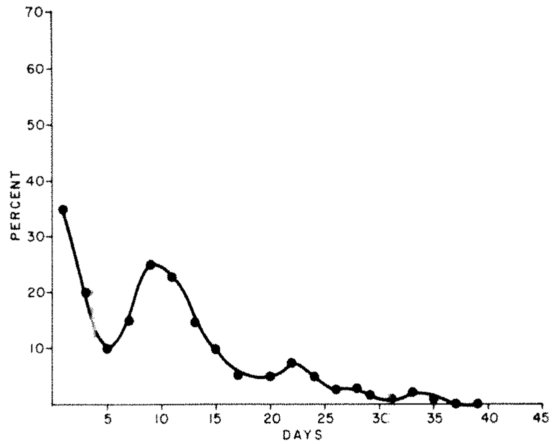

Fig. 3. Median percentage values indicating the number of exfoliating malignant cells during treatment in relation to the number of benign squamous cells in oral smears (40 patients).

During the first few days of therapy there was usually a gradual decrease in the number of cancer cells, characteristically followed by an increase sometime between the seventh and fifteenth days, and not infrequently exceeding the number in the pretreatment smears. This was then followed by a more gradual, but still fluctuating decline. The temporary increase in malignant cells above the pretreatment levels is believed to be the result of decreased cohesiveness rather than stimulation of tumor growth, since the percentages of poorly differentiated cells were not coincidentally increased as would be expected if the latter were true.[22]

There were certain factors which appeared to influence the extent of exfoliation, namely, size, location, gross anatomic type, and the degree of differentiation of

the neoplasms. In general, large, exophytic or poorly differentiated carcinomas exfoliated more than did small, ulcerated or well-differentiated carcinomas. Significant factors would seem to be the size of the tumor surface area, the presence or absence of an inflammatory pseudomembrane (covering ulcerated tumors) which restricts the detachment of malignant cells, and the degree of intercellular adhesiveness which is undoubtedly less in poorly differentiated neoplasms. It must be admitted that some of the cells from very well-differentiated carcinomas may have been mistaken for benign cells. Location also played a role, malignant cells being more abundant in carcinomas of the floor of the mouth than in other locations, even though the tumors of the floor of the mouth were, on the average, smaller and less exophytic than those in other areas.

Although the above factors obviously had some bearing on the extent of exfoliation, even the combination of all of the factors could not adequately explain the differences. For example, tumors which appeared to be identical in location, size, and gross and histologic type often produced completely different smears, one set containing abundant malignant cells, the other practically none. The vigor applied to scraping the surface or the selection of surface to be scraped was not a significant factor, for, if this had been the case, there should have been much greater variation from day to day in individual cases. On the contrary, each patient showed remarkable uniformity in his pattern of exfoliation. The cells may have been more numerous in smears from neoplasms of the floor of the mouth due to trapping of the cells in the dependent portions of the oral cavity, but, then again, exfoliation from some of these neoplasms was minimal.

Our initial observations[12] indicated that neoplasms which exfoliated abundantly were more likely to metastasize than those which did not, as was also noted by Graham[6] in carcinomas of the cervix. Since this feature should indicate lack of cohesiveness, it may also indicate a greater propensity for the cells of such tumors to break off and enter the lymphatics.[12] Our later findings have only partly sustained these observations. Although the median exfoliation of 15 patients who developed metastasis was 15 per cent, while that of 24 patients who have not demonstrated metastases to date was only 5 per cent, the number of profusely exfoliating neoplasms which metastasized (39 per cent) was only slightly greater than the poorly exfoliating neoplasms (29 per cent). These slight differences are probably explained on the basis of better cellular differentiation of more of the poor exfoliators, since it is well known that less well-differentiated carcinomas are more likely to metastasize.

CONVERSION OF SMEARS FROM POSITIVE TO NEGATIVE

A few of the largest neoplasms maintained dense populations of malignant cells throughout treatment, but this was the exception rather than the rule. In most instances the cancer cells became so sparse during the last two to three weeks of treatment that they became difficult to find, there often being only one or two in an entire smear, despite the usual number of benign superficial squamous cells and inflammatory cells. Interpretation also became more difficult, and occasionally it was impossible to differentiate between well-differentiated squamous carcinoma cells and benign squamous cells showing radiation changes, thus necessitating the use of a "suspicious" category.

Over 70 per cent of the patients still had positive or suspicious smears at the end of treatment, almost 50 per cent being unequivocally positive (Table II). These cytologic findings correspond well with the histologic observations of Hall and Friedman,[7] who found persistent tumor in 50 per cent of biopsies from irradiated carcinomas of the mouth or oropharynx.

Graham and Graham[5,6] noted that the presence of malignant cells in vaginal smears at the completion of treatment did not preclude cure, and our findings were

Table II

COMPARATIVE VALUE OF ORAL SMEARS AT COMPLETION OF TREATMENT AND ONE TO TWO MONTHS AFTER IRRADIATION

Clinical Status	End of Treatment (55 patients)			Immediate Postirradiation Period (47 patients)		
	Positive	Suspicious	Negative	Positive	Suspicious	Negative
No neoplasm	8	7	6	0	2	17
Primary	14	5	9	13	2	7
Residual neoplasm	9	4	7	9	2	3
Recurrence	5	1	2	4	0	4
Metastases	10	4	4	5	4	6
Dead	9	1	4	6	3	1
Total patients	24	15	16	13	6	28

similar. Eighteen patients who had positive or suspicious smears at this time converted during the immediate postirradiation period (one to three months). Most of these conversions occurred during the first post-irradiation month, the tardiest conversion being between the second and third month. The lack of correlation between the presence or absence of malignant cells at the end of treatment and the clinical results is illustrated in Table II. It is readily apparent that smears taken at this time are of relatively little prognostic value, especially if positive.

The significance of the results of examination of smears taken within the first three months following completion of treatment is indicated in Table II, and is in striking contrast to that of the examinations made at the end of therapy. Each of the 13 patients who had positive smears during the postirradiation phase either had residual neoplasm or developed recurrent neoplasm, and 6 have died; only 3 (11 per cent) of the 28 patients whose smears were negative during this phase had residual tumor; only 4 of these 28 subsequently developed recurrent neoplasm, and all but 1 are alive at the time of this report.

DETECTION OF RECURRENT NEOPLASM

Eight patients had what was clinically regarded as recurrent neoplasm. However, 4 of these had positive smears throughout the postirradiation period and their neoplasms are therefore believed to represent residual rather than recurrent carcinoma. The other 4 had negative smears immediately after irradiation; 1 remained negative, 1 reconverted to positive and 2 changed from negative to suspicious when the recurrence developed. The fact that there was only 1 false-negative is heartening, since it was feared that many of the recurrent neoplasms might be entirely submucosal and would, therefore, escape cytologic detection.

INFLAMMATORY CHANGES

Practically all of the smears which contained malignant cells also contained innumerable leukocytes and bacteria, including many within benign and malignant squamous cells, and there was usually a proportionate decrease in the inflammatory cells as the number of malignant cells diminished. The leukocytes were predominantly neutrophilic granulocytes in the pretreatment smears and in those taken during the early phases of treatment, while eosinophilic leukocytes, lymphocytes, and plasma cells appeared in increasing numbers during treatment. The persistence of inflammatory cells after the disappearance of malignant cells usually indicated persistence of ulcers and, when found in postirradiation smears, which were devoid of malignant cells, suggested ulcerative radio-

necrosis. Most of the post-treatment smears from patients without clinical evidence of residual neoplasm were characterized by their tidy, clean appearance, since they consisted exclusively of superficial squamous cells which showed none of the marked degenerative changes seen during and before treatment and were not accompanied by leukocytes, bacteria, and debris. In several instances, recurrent neoplasm was first suspected when a patient whose previous smears had this uninfected appearance suddenly developed smears containing many leukocytes, even in the absence of malignant cells, the latter being found in subsequent smears.

The presence of erythrocytes was less constant and seemed to be related to the vigor used in scraping the lesions. In no instance was bleeding severe enough to interfere with the interpretation of the smears, to require treatment, or to impair healing.

CONCLUSIONS

1. The radiation changes in benign and malignant squamous cells from oral or oropharyngeal carcinomas have been described; these include observations of the nucleic acids by acridine-orange fluorescence microscopy.

2. The radiation response of benign squamous cells was not found to be of practical value in prognosticating the clinical results.

3. *Destruction* of malignant cells by irradiation appears to be more important than radiation-induced tumor *differentiation*.

4. Determination of maturation and cornification indices were of no practical clinical value.

5. Percentage analysis of Caspersson type A and type B cells during treatment correlated well with clinical results.

6. There were marked differences in the exfoliation of malignant cells from neoplasms which were otherwise similar in location, size, gross characteristics, and histologic differentiation. The reasons for these differences remain to be elucidated. Initially reported increased propensity for abundantly exfoliating tumors to metastasize was only partially substantiated.

7. The presence of malignant cells in oral smears taken at the end of treatment does not preclude irradiation arrest, and many patients showed conversion of positive to negative smears following completion of treatment.

8. Oral smears taken during the first three months after treatment are of practical prognostic value. Every patient whose smears were positive during that period was ultimately proved to have residual or recurrent neoplasm, while only 11 per cent of patients with negative smears at that time had residual neoplasm.

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250 KV. ROTATION THERAPY FOR CARCINOMA OF THE ESOPHAGUS USING THE JOHNS HOPKINS SCREEN INTENSIFIER*

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RADIATION therapy by rotation for malignant disease is not a new concept. However, due to the work of Dr. Jens Nielsen[6] of Copenhagen, this form of treatment has become quite popular in recent years, particularly in Scandinavian countries.[3,4] The principle of Nielsen's method of therapy is that the patient is rotated in an extremely narrow beam of radiation, sometimes as small as 1 cm. wide, with the lesion centered at the axis of rotation. The lesion is identified and is watched throughout the treatment time on a fluoroscopic screen, the position of the patient being altered during treatment if the lesion should go out of the field. In this fashion, the skin is spared by using the whole circumference of the body; the integral dose is kept low; the normal tissues are spared as much as possible; and the volume of tissue being treated receives the maximum dose. Even using radiations in the 250 kv. range, a cancerocidal dose can be delivered with this technique. Other methods of rotating the patient or the machine have been developed, but with no other technique can such a narrow field be used or such good control of the treatment area be obtained.

The modification of Nielsen's method which has been adopted at The Johns Hopkins Hospital is in the use of the fluoroscopic screen intensifier with a televised image for control of the treatment zone. This excludes exposure of personnel watching the direct screen through the control window, and obviates the elaborate mirror systems which have been devised with the same end in view. Dark adaptation by the observer is also no longer necessary.

Figure 1 shows a patient seated on a rotating chair with the roentgen-ray machine and screen intensifier in position. Figure 2 shows the viewing panel situated in the control room on which the operator can watch the image throughout treatment without himself being exposed to the radiation. This arrangement was described by Morgan *et al.*[5] as a logical area of usefulness for the screen intensifier and, although not essential to the use of rotation therapy, it has proved to be of tremendous value in determining the accuracy of direction of the beam of radiation and in ensuring centralization of the beam on the desired area.

When the lesion under treatment is a carcinoma of the esophagus, the patient sits on the rotating chair with the axis of rotation at 75 cm. from the focal spot of the 250 kv. roentgen-ray machine and the screen intensifier is placed at the far side of the

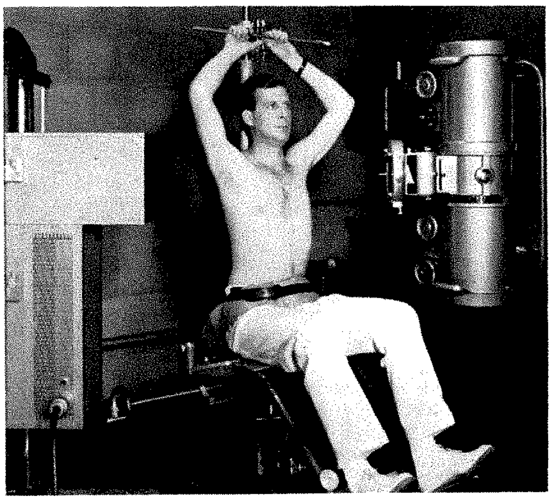

FIG. 1. Patient positioned for rotation therapy.

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‡ Radiologist in Chief, The Johns Hopkins Hospital.

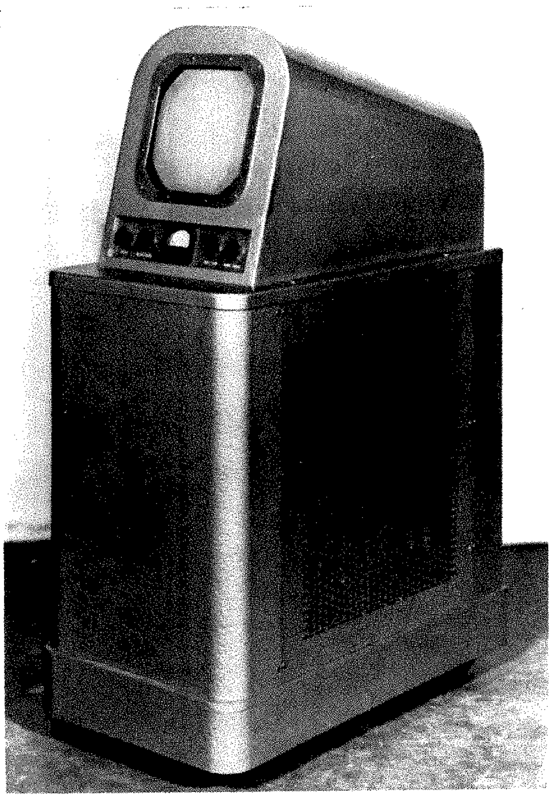

Fig. 2. Viewing panel of screen intensifier.

patient. The patient is given a mouthful of barium to be retained in the mouth; the chair is set in motion and, when roentgen rays are generated, the image of the chest appears on the television screen. Instructions are then given to the patient to swallow the barium. The opaque material is visualized on the screen and should remain in the center of the beam throughout the rotation. If it does not do so, the position of the chair is altered accordingly. The chair rotates at a speed of two revolutions per minute and, initially, a total of ten revolutions, or five minutes of treatment time, is given in order to familiarize the patient with the procedure. When the dosage calculations are completed, an estimated tumor dose of 200 r is given daily. These calculations are made during the therapy and will be further discussed below. The size of the treatment field is usually 5 cm. in width at the rotational axis and is of a length corresponding to three times the roentgenologic estimate of the involved area of the esophagus. Because of the angulation of the esophagus in its lower third, lesions of this area naturally will require a wider beam of radiation. The factors used are 250 kv., 0.5 mm. Cu+1.0 mm. Al filter, tumor target distance 75 cm. The half value layer of the beam in current use with these factors is approximately 2.0 mm. Cu. The tube is specially made by the Machlett Company with a very small focal spot of 0.5 cm. diameter, which gives excellent resolution of the image on the television screen.

SELECTION OF PATIENTS

Not all cases of carcinoma of the esophagus have been deemed suitable for treatment by rotation therapy. The full course, lasting some six weeks, entails a not inconsiderable constitutional strain on the patient and we have felt that the general condition of the patient should be moderately good to allow for completion of the treatment. In one instance, conventional anterior and posterior opposing portals were used to reduce the esophageal obstruction and three months later, when the patient's physical condition had improved, a course of rotation therapy was instituted.

The second criterion for treatment by this method which we adopted is the absence of obvious metastatic disease. It was felt that, if the patient has a life expectancy of only a few weeks, there is no justification for a type of therapy which, at best, can only control the primary disease. In such cases, palliative therapy was given with a suitable number of fixed fields and symptomatic metastases were irradiated in a similar fashion.

Thirdly, in lesions of the upper and lower thirds of the esophagus, surgical opinion was sought and all the cases treated by rotational therapy were deemed inoperable by the surgical staff. Several lesions of the middle third of the esophagus, which probably were resectable, were referred for roentgen therapy in order to compare the results of such treatment with those obtained by the formidable operative proce-

dures necessitated by the site of the lesion. The extent of the involvement of the esophagus *per se* was not considered to be a contraindication to radical roentgen therapy in the absence of demonstrable metastases in a patient in fair general health.

TREATMENT TIME AND DOSAGE

Allowing for the initiation of the patient to the procedure and for the time taken in calculating the dosage to the esophagus, a dose rate of approximately 1,000 r per week given in five treatment days was adopted, and a calculated tumor dose of between 5,500 and 6,000 r in five to six weeks was given in most cases.

Many methods of calculating the tumor dose have been described. Most simply, one can take an average measurement of the body diameter at the level of the treated lesion and estimate the dosage from isodose curves and depth dose tables after suitable allowance is made for absorption in the lung tissue. This is unsatisfactory because of the irregularity of the body surface and the difficulty in arriving at an estimate of average transmission through the intrathoracic structures and thoracic wall. Measurements in a phantom constructed to conform to the shape of the body have the same objection.

Wachsmann and Barth[10] devised a calculation system based on the ratio of the transmitted dose rate at a point twice the rotational axis-target distance to the air dose rate at the rotational axis. From a nomogram prepared for the specific physical factors used, the localized percentage tumor dose at the rotational axis can be determined. If the tumor is located at the axis, this then becomes the tumor dose. Theoretically, this seems sound and this method of dosage calculation was employed in the early cases in our series. An attempt was made to obtain a check of this calculation by the use of dosimetric film swallowed by the patient during the rotation treatment and it was found that an approximate correlation was obtained. Subsequently, we obtained a Bomke direct reading dosimeter with an ionization chamber contained at the tip of a narrow bore flexible rubber tube. In theory, this could be placed at the center of the lesion during the rotation and a direct reading obtained of the dose delivered at that point. Unfortunately, in the majority of our patients, the degree of esophageal obstruction was such that they were unable to swallow this tube in the initial stage of their course of therapy. However, we were able to obtain direct readings in 6 patients and, in these, a high degree of correlation was obtained between Bomke measurements and calculation of dosage by the Wachsmann-Barth method. A Siemens dosimeter swallowed by the patient has also given similar readings in 4 patients.

We have, therefore, used the transmission dose method of calculation in the belief that it is an accurate, simple and satisfactory method of dosimetry. It is intended that when further experience is obtained a more detailed report of our dosimetric calculations will be published.

MATERIAL

During the past six years, a total of 57 patients with midline thoracic tumors has been treated by rotational therapy with the image intensifier (Table 1). Of these, 45 patients with carcinoma of the esophagus represent by far the largest group. Three of these were unable to complete the course of therapy; 2 had lesions of the cardia with intrathoracic spread and a third had a bypass operation in which the diseased esophagus was left in place. In this latter patient it was found that irradiation of the esopha-

Table I

CARCINOMA CASES TREATED

Site	No.
Esophagus	45
Lung	7
Pharynx	4
Trachea	1
Total	57

Table II

CARCINOMA OF ESOPHAGUS
AGE AND SEX DISTRIBUTION

Age	No. of Cases	Sex		No. of Cases
38	2	Male		39
40–49	7	White	22	
50–59	18	Negro	17	
60–69	13	Female		6
70–79	3	White	3	
84	2	Negro	3	
Average age, 59.4 years				

gus was limited by the presence of a loop of small intestine which had been brought into the chest. One further patient has only recently completed his course of treatment. Thus 41 patients who have had a full course of therapy at least six months ago are available for evaluation.

The age and sex of these patients are shown in Table II. It will be seen that the majority were males and that the highest incidence was during the sixth and seventh decades of life. The histology of the lesions and the site in the esophagus are shown in Table III. Three patients were treated without obtaining a positive biopsy but the clinical and roentgenologic picture was such that there was little doubt of the diagnosis. The greatest number of patients had lesions

Table III

CARCINOMA OF ESOPHAGUS
SITE AND HISTOLOGY

Site in the Esophagus	No. of Cases
Upper Third	5
Middle Third	33
Lower Third	5
Whole Esophagus	2
Histology	
Squamous	35
Adenocarcinoma	2
Undifferentiated	5
Unknown	3

Table IV

CARCINOMA OF ESOPHAGUS
DOSAGE

Dose (r)	No. of Cases
Less than 5,000	7
5,000 to 5,490	6
5,500 to 5,990	12
6,000 and more	20

of the middle third of the esophagus, but a few with lesions of the upper and lower thirds of the esophagus were also treated, and 2 patients had involvement of almost the entire esophagus.

Table IV groups the patients according to the calculated dosage received in the esophagus. Those receiving less than 5,000 r include the 3 who did not complete their course of therapy. The lowest dose given for attempted radical treatment was 3,600 r administered in thirty-four days to an elderly patient who had extensive involvement of the lower and middle thirds of the esophagus. The highest dose recorded was 6,175 r delivered in thirty-five days.

RESULTS OF TREATMENT

SURVIVAL

The survival time of the 41 patients under consideration is shown in Table V. Of the patients who survived more than two years, 1 died thirty-two months after his initial therapy, having developed enlarged mediastinal lymph nodes which were temporarily relieved by the administration of

Table V

CARCINOMA OF ESOPHAGUS
RESULTS

Survival Time (mo.)	Dead	Alive
Less than 6	17	—
6–12	13	3
12–24	3	2
More than 24	2	1
Average survival, all patients		8.7 months
Average survival, patients dead		8.4 months
Average survival, patients alive		10.0 months

external irradiation. He at no time had difficulty in swallowing after treatment but he was troubled by eructation of gas for the last two years of his life. No autopsy was performed on this patient. A second man survived twenty-nine months from the beginning of treatment. He had developed a stricture of the esophagus following treatment which allowed only soft foods to pass. He fed himself largely through a gastrostomy and, after two years without evidence of recurrent disease, it was decided to attempt to dilate the stricture in the upper third of the esophagus. Unfortunately, subsequent to this procedure, he perforated his esophagus at the site of the stricture, developed mediastinitis and died. At autopsy there was no evidence of tumor at the site of the stricture nor of any metastatic disease. A third patient has survived for more than twenty-four months and is still doing very well without any evidence of recurrence.

The average over-all survival of our patients is 8.7 months but at least 3 of the survivors appear to be very well and it is probable that they will survive for several months more. Of those who are dead, the average survival is only 8.4 months and of those still living the average is now ten months. The survival rates are extremely poor but they are at least comparable with those obtained by other modalities in the treatment of carcinoma of the middle third of the esophagus.[1,2,7,8,9] It is submitted that this type of therapy of this lesion will provide a life expectancy comparable with that obtained by a radical surgical procedure[2,8,9] and without the very high mortality associated with operations in this area. Supervoltage therapy has not extended life expectancy significantly beyond that obtained in this series.[1]

The mode of death in those patients who have succumbed is of some interest (Table VI). There was evidence of widespread metastatic disease in no fewer than 15 of these patients. In none was there tumor recurrence at the site of the primary lesion and the majority of these patients were able to swallow relatively normally for the months of life remaining to them. There was definite evidence of local recurrence which led to death in 4 patients and of local recurrence with perforation and subsequent death in 4 others. One patient developed a fistula following esophagoscopy but did not have evidence of disease. Six patients developed strictures at the site of the lesion which contributed to their deaths in that it was not possible to keep the esophagus patent. Four patients subsequently developed lesions elsewhere in the esophagus; 3 of these were at the cardia and 1 in the mid-esophagus, the latter being in a patient who had previously received therapy for a lesion of the upper third of the esophagus.

TABLE VI

CARCINOMA OF ESOPHAGUS
MODE OF DEATH

	No. of Cases
Metastatic Disease	15
Local Recurrence	4
Fistula	5
Stricture	6
Recurrence Elsewhere	4
Unknown	1

One particularly interesting case was a sixty-five year old Negro male who was admitted to the hospital in July, 1955, with almost complete obstruction of the middle third of the esophagus. His general condition was poor and it was decided that he could not tolerate a full course of rotational therapy. He was given a tumor dose of 2,500 r through anterior and posterior fields with dramatic improvement in his symptoms. He was able to swallow without great difficulty and in September his condition had improved to the extent that he was judged to be suitable for radical treatment. A tumor dose of 4,750 r was given in thirty days by rotational therapy, the previously treated areas being shielded with lead during the rotation. His swallowing became almost normal and, at esophagoscopy subsequent to the treatment, no abnormality

was noted. In November, 1956, one year later, he was readmitted to the hospital with symptoms of obstruction and was found to have a polypoid lesion at the cardiac end of the esophagus. On November 5, 1956, this was resected and the stomach was anastomosed to the upper end of the resection which by measurement was proved to have been within the area irradiated one year previously. At the line of section there was no evidence of malignant disease and only minimal changes of radiation fibrosis could be seen. The anastomosis healed well and the patient began to swallow again quite normally. On January 25, 1957, he was found dead in bed at his home. Unfortunately, an autopsy was not obtained but he had been seen by a friend on the previous evening and was then apparently quite well. It is felt that he probably had a cardiovascular accident but a breakdown of the suture line cannot of course be excluded.

COMPLICATIONS

In Table VII are shown the complications which occurred in this series of patients. Six of our cases developed strictures at the site of the primary lesion following the course of treatment, these strictures being sufficiently severe to impede the swallowing of solid foods. One stricture was resected and the tissue showed evidence of dense fibrosis but no active tumor (Fig. 3 and 4). In 1 case, an attempt to dilate the stricture two years following the completion of therapy led to a perforation and subsequent death. In the other 4 patients, gentle dilatation of the stricture kept the esophageal lumen temporarily patent but subsequent dilatation became increasingly necessary and the patients gradually succumbed from inanition and cachexia. One woman was enabled to swallow for a period of fifteen months following treatment with dilatation at approximately weekly intervals. In retrospect, a resection of the fibrotic area might have been beneficial but, in 4 of the patients, the primary lesion was at the level of the arch of the aorta and it was felt that

TABLE VII

CARCINOMA OF ESOPHAGUS COMPLICATIONS

	No. of Cases
Stricture	6
Fistula	5
Pneumonitis	1

resection would have been impossible. Alternatively, a bypass operation might be considered.

Five patients in our series developed fistulae at the site of the primary lesion subsequent to treatment. In those cases in which autopsies were performed, there was evidence of persistent tumor at the site and in 3 of these the fistulous openings were into major blood vessels closely adjacent to the esophagus. This complication is of

Fig. 3. Specimen of carcinoma of esophagus five months after administration of 5,500 r.

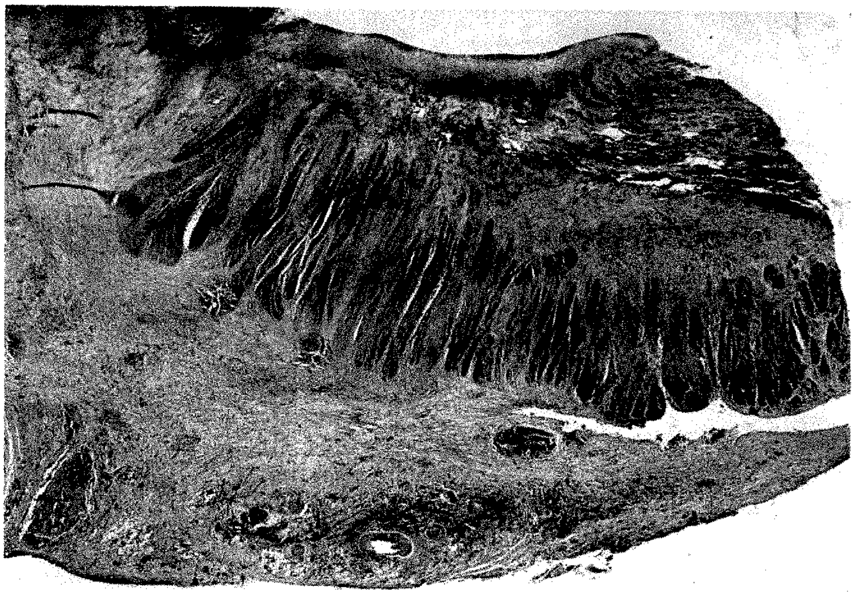

Fig. 4. Same specimen as in Figure 3 showing gross fibrosis but no active tumor.

course a common one in lesions of the middle third of the esophagus which are not treated.

Perhaps unexpectedly, the finding of severe radiation pneumonitis was confined to 1 case. A transient shadow was seen in the pulmonary parenchyma in 1 patient but he was entirely asymptomatic. The patient who did develop pneumonitis was greatly distressed by dyspnea but his symptoms rapidly cleared under steroid therapy. He subsequently developed a spontaneous pneumothorax which was treated by drainage with complete re-expansion of the lung. The etiology of this complication is not clear. In none of the 41 patients, nor in fact in any of the patients treated by this technique, was the constitutional upset associated with radiation therapy a problem sufficient to warrant interference with the normal course of therapy. The occasional slight nausea in a few patients was readily controlled by the administration of one of the antiemetic preparations.

POST-THERAPY ESOPHAGOSCOPY

Many patients have in the past been treated by radiation therapy but there are few observations in the literature on the local results of treatment or the effect on the esophagus. When a stricture was excised in 1 patient early in this series, it was clear that the esophagus, exclusive of the stricture, was quite healthy and we felt that little harm could ensue in other patients from esophagoscopy following treatment. Accordingly, four weeks after completion of treatment, several of these patients were subjected to esophagoscopy and biopsies were taken from the area where the tumor had originally been identified. These results will be published separately. A total of 14 patients were esophagoscoped subsequent to treatment and the biopsies were entirely negative, showing only scarring, in all but 1 of these. The patient who showed a positive biopsy after treatment died of his disease three months later. In all of the cases a characteristic circumferential contraction of the esophageal lumen, with smooth walls, was seen. A bougie was passed through this constriction which was found to be readily distensible. Biopsies were then taken from the area below the constriction. No complications ensued from this procedure and, while a negative biopsy is of little significance, a positive finding soon after treatment is obviously a useful

prognostic indicator and it is felt that this procedure is of considerable value.

DISCUSSION

During the past six years, some experience has been gained in the treatment of lesions in the midline of the body, chiefly carcinoma of the esophagus. Using a screen intensifier technique with televised image, it has been possible to follow the lesion throughout the course of treatment on the screen and thus to reduce the width of the treatment field and to ensure that the lesion is within the treated area at all times. Greatest experience has been gained with lesions of the middle third of the esophagus, it being felt that the very high mortality associated with the surgical resection of lesions in this area did not justify operative treatment. The survival of the patients treated with the technique described in this paper cannot be considered satisfactory but the palliative value of the treatment is certainly substantial, since the great majority of the patients were able to swallow normally for the remainder of the time that was left to them.

It is felt that this relatively simple procedure affords better palliation than surgery and, although no long term survivals have yet been obtained with this technique, late recurrence at the site of the lesion has not occurred. Those who have died after long periods of freedom from disease have done so either from metastases which would not have been prevented by surgery or, in 1 instance, by an over-enthusiastic attempt at dilatation of an incomplete stricture. No patient died as a result of the procedure and the complications arising from the treatment are those common in untreated carcinoma of the esophagus or are relatively insignificant in relation to the seriousness of the primary disease. Radiation pneumonitis was not a serious complication except in 1 patient and in his case the period of morbidity was only about two weeks.

This technique has, in this hospital, been used in association with a 250 kv. machine and it is difficult to believe that with supervoltage any better results will be obtained. However, the screen intensifier technique can be readily employed with a 2 mev. machine with a small focal spot. This no doubt is a rational extension of the technique but in this series the tumor dose to be delivered to the primary lesion has never been limited by the skin reaction or by the development of pneumonitis.

SUMMARY

1. The use of the Johns Hopkins screen intensifier in the treatment of carcinoma of the esophagus by rotational therapy with a 250 kv. machine is described.

2. With this technique a very narrow beam of radiation can be used and treatment of the desired area throughout the course of therapy can be ensured.

3. The results of this treatment over a period of six years are not gratifying in terms of survival but the palliative effect of the treatment is at least as good as that associated with surgical resection or with other methods of radiation therapy. Furthermore, there is no mortality associated with this procedure and, when a larger series of patients is treated, it is confidently expected that an occasional long term survivor will appear.

4. The possible value of post-treatment esophagoscopy is discussed. In a series of patients so investigated no complications ensued.

5. The problem of dosimetry in rotational therapy is also discussed briefly and it is concluded that the transmission dose calculations give a value closely approximating the true tumor dose as measured by an ionization chamber placed at the site of the lesion.

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ENDOBRONCHIAL MALIGNANT LYMPHOMA*

REPORT OF FIVE CASES IN ADULTS

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THE pulmonary manifestations of malignant lymphoma have been fully described in the literature with respect to mediastinal disease, pleural involvement and parenchymal infiltration. The small number of reports concerning endobronchial invasion with atelectasis has attracted the present authors' attention. The majority of these deal with isolated cases and, insofar as we have been able to determine, only 2 cases have been previously reported in the radiologic literature.[7,8] Soulas[8] described an interesting case of obstructive emphysema secondary to partial occlusion of the right mainstem bronchus by Hodgkin's granulomatous tissue. He performed 4 bronchoscopic studies over a ten month period and only the fourth biopsy was diagnostic of Hodgkin's granuloma, showing Reed-Sternberg cells. A case of complete occlusion of the left mainstem bronchus by Hodgkin's granuloma was reported by Paviot *et al.*[6] The occlusive mass appeared at postmortem examination as coagulated mucus but microscopic examination disclosed a true granuloma. In a case presented by Heatly,[3] atelectasis of the right lower lobe was found to be caused by a smooth, slightly reddish mass resembling a bronchial adenoma. Although the biopsy of this mass was suggestive of lymphoma, a thoracotomy was required to establish a positive diagnosis of Hodgkin's disease. Hardin's[2] case illustrated a progressive atelectasis of the entire right lung with intermittent relief following irradiation of the mediastinum. The radiation dose was not specified and the disease subsequently became refractory to this form of therapy.

The article by Moolten[5] presents an accurate description of the pathologic nature of pulmonary Hodgkin's disease. Detailed postmortem study was reported in 8 cases and in 4 granulomatous infiltration of the bronchi was demonstrated. In a fifth case, a polypoid mass projected into and completely occluded the right mainstem bronchus. This was thought to result from an unusual accident of growth which altered the course of the disease and produced early death.

We have encountered 5 cases presenting this complication and do not regard it as an unusual growth variant. Rather, it should be considered a true facet of systemic lymphomatosis, the developement of which may be facilitated by initially inadequate irradiation of the mediastinum.

The pertinent data referable to the pulmonary aspect of these cases are presented in the following case histories and the radiation therapy data are given in Table I.

REPORT OF CASES

Case I. R. G., a thirty year old Negro female, was admitted to the M. D. Anderson Hospital on January 3, 1957, with chief complaints of progressive dyspnea and severe, irritating nonproductive cough of one month's duration.

A diagnosis of generalized Hodgkin's disease was established on June 3, 1954, on the basis of cervical and mediastinal lymphadenopathy and a positive right cervical lymph node biopsy. On July 15, 1954, radiation therapy was started and 1,200 r was delivered to the mediastinum through parallel opposing fields and an additional 1,500 r to the right neck. Treatment was completed to both areas over a sixteen day period. On February 8, 1955, the mediastinum was re-treated for recurrence. A dose of 2,000 r

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TABLE I

ROENTGEN THERAPY DATA

Patient		Tumor Dose	Survival Post Irradiation	Cause of Death
Case I* R.G.	(a) 250 kv., H.V.L. 3.1 mm. Cu (b) Betatron	1,900 r 1,100 in 5 wk.	9 mo.	Acute congestive heart failure; no postmortem examination
Case II L.L.	250 kv., H.V.L. 3.1 mm. Cu	2,030 r in 36 da.	8 mo. follow-up, negative chest roentgenogram but aggressive disease present in other areas	Lost to follow-up
Case III† V.E.	(a) Rotational 220 kv., H.V.L. 2.75 mm. Cu (b) 250 kv., H.V.L. 3.1 mm. Cu	2,000 r in 24 da. 2,050 r in 24 da.	18 mo.	Peritonitis from perforated peptic ulcer, prepyloric; residual endobronchial disease
Case IV J.V.B.	250 kv., H.V.L. 3.1 mm. Cu	2,100 r in 38 da.	6 mo. follow-up, negative chest roentgenogram but aggressive disease present in other areas	Lost to follow-up
Case V E.Y.	250 kv. grid H.V.L. 1.1 mm. Cu	2,400 r in 38 da.	15 da.	Uncontrolled congestive failure, myocardial tumor infiltration; thrombosis of superior vena cava

* Previously administered therapy for mediastinal lymphadenopathy: 1,200 r at 250 kv. in 16 days in July, 1954; 2,000 r at 250 kv. in 10 days in February, 1955.

† Previously administered therapy for mediastinal lymphadenopathy: 1,200 r in air to each of 15×15 cm. anterior and posterior ports in 1950.

was delivered through parallel opposing anterior and posterior ports over a ten day period.

Physical examination revealed an acutely ill female extremely dyspneic and coughing at frequent intervals. Moderate discrete, firm, nontender lymph nodes were noted in the left cervical, axillary and supraclavicular areas. Coarse ronchi were heard over the right chest and there was dullness with absent breath sounds over the entire left chest. The liver was 2 fingerbreaths enlarged and the spleen not palpable.

The clinical impression of atelectasis of the left lung was confirmed by a chest roentgenogram (Fig. 1*A*). Bronchoscopy disclosed complete closure of the left mainstem bronchus at the level of the carina by an irregular growth of firm, nodular, grayish-white tumor tissue. The biopsy specimen from this area showed an atypical lymphatic infiltrate compatible with malignant lymphoma.

The patient was placed in an oxygen tent on the day of admission because of severe dyspnea and six days later radiation therapy to the mediastinum was started. After one week of therapy, marked improvement allowed discontinuation of oxygen. A total dose of 3,000 r was given over a period of five weeks. A roentgenogram of the chest at the completion of therapy showed complete aeration of the left lung and the patient was discharged (Fig. 1*B*).

Six months later, the patient was re-admitted in a terminal condition and expired on the third hospital day. A portable chest roentgenogram showed only a left pleural effusion. Permission for postmortem examination was denied.

CASE II. L. S., a forty year old Negro male minister, was admitted to the M. D. Anderson Hospital on June 1, 1956, with complaints of severe weakness, dyspnea, a dry irritating cough and edema of both lower extremities of several weeks' duration. A diagnosis of lymphosarcoma was established eleven months previously.

On physical examination, dullness and absent breath sounds were noted over the entire left lung. There was a suggestion of several deep

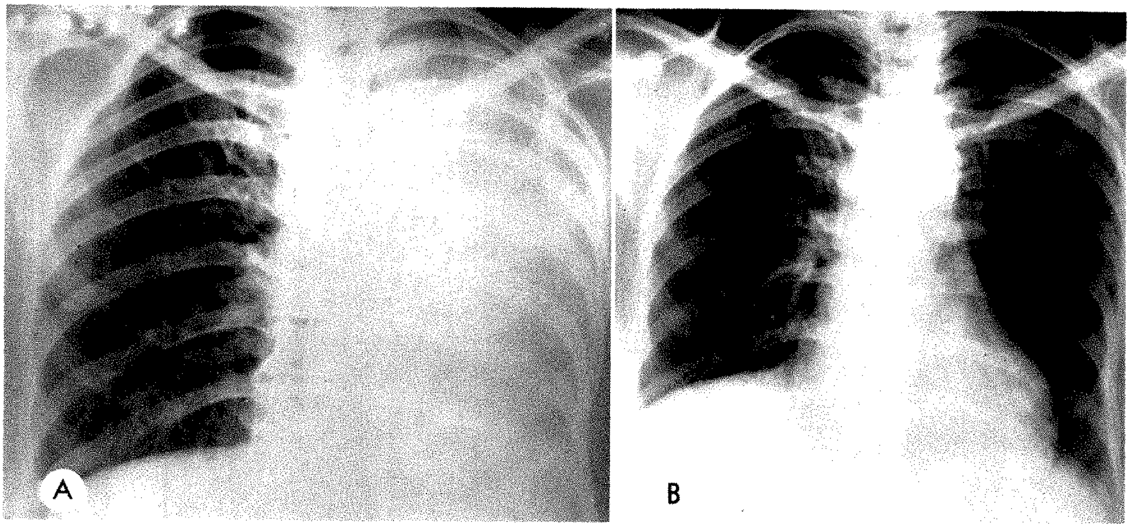

Fig. 1. Case i. Endobronchial Hodgkin's disease. (*A*) Atelectasis of the left lung. (*B*) Complete re-expansion of the lung following roentgen therapy. (The findings were identical in Case ii.)

masses in the midabdomen though the liver and spleen were not enlarged. A roentgenogram of the chest demonstrated massive opacification of the left lung field with a shift of the heart and mediastinum to the left. Bronchoscopy showed complete occlusion of the left mainstem bronchus about 1 cm. below the carina by a firm mass of grayish-white tumor tissue. This was biopsied and histologic examination revealed a white cellular infiltrate of lymphomatous character. Although Reed-Sternberg cells were not seen, the general pattern of the tumor suggested Hodgkin's disease.

Radiation therapy was given through anterior and posterior mediastinal fields for a minimal dose of 2,030 r in thirty-six days. After two weeks of therapy, dyspnea was considerably improved. After three weeks of therapy, a roentgenogram of the chest showed complete re-expansion of the left lung.

Two months following discharge, the patient was admitted again to the hospital with complaints of extreme weakness and subcutaneous nodules over the chest, abdomen and groin. Physical examination disclosed the presence of hard subcutaneous nodules scattered over the chest and abdomen, measuring from 1 cm. to 5 cm. in diameter. A biopsy of one of the abdominal nodules showed an atypical lymphatic infiltration compatible with lymphosarcoma. A repeat chest roentgenogram showed both lungs to be expanded with no evidence of mediastinal lymphadenopathy. Therapy consisted of 40 mg. of nitrogen mustard intravenously in one dose. The patient was discharged twelve days later at his own request with no improvement noted. Six months later progression of the skin nodules was noted, but a chest roentgenogram was negative. This patient, unfortunately, has been lost to follow-up and is presumed dead.

Case iii. V. E., a forty-five year old housewife, was admitted to the M. D. Anderson hospital on November 24, 1954, with complaints of progressively worsening dyspnea and dry cough of five months' duration.

A diagnosis of Hodgkin's disease was established during October, 1957, at another hospital by cervical lymph node biopsy. Radiation therapy was given at the same institution to the mediastinum and we were informed that the dose was 1,200 r in air to anterior and posterior fields over a period of twenty-one days.

Physical examination revealed an ill-appearing middle-aged white female having considerable difficulty breathing. Ronchi and wheezing were noted over both lung fields. Small shotty lymph nodes were found in the cervical, axillary and inguinal areas. The liver and spleen were not enlarged. A chest roentgenogram showed a large mediastinal mass, predominantly left sided, and a definitely enlarged right hilar shadow. The transverse measurement of the mass was 18 cm.

On November 25, the day following admission, 30 mg. of nitrogen mustard was given intravenously in a single dose and within two days dyspnea was much improved. The patient

was discharged on the seventh hospital day and seen in the out-patient clinic two weeks later. She was virtually free of symptoms except for mild nausea. A repeat chest roentgenogram showed regression in the size of the mediastinal mass from 18 cm. to 12 cm.

During the next four and one-half months, the clinical situation remained unchanged. After this period, a progressive increase in the mediastinal mass was observed with no associated symptoms. It was decided to re-treat the mediastinum with radiation therapy. Using 220 kv. rotational therapy, 2,000 r was delivered to the mediastinum over a twenty-four day period ending June 10, 1955. Serial chest roentgenograms demonstrated no significant regression of the mediastinal mass, and on September 14, the patient was re-admitted and 50 mg. of nitrogen mustard was given in one dose. After seventeen days of hospitalization, she was discharged to the out-patient clinic. Although a significant diminution occurred in the size of the mass, it was less than the first nitrogen mustard induced response. This remission lasted four months after which an irritative cough and exertional dyspnea occurred. However, she was not re-admitted until October 12, when cough and dyspnea were severe at rest and associated with left pleural effusion. A chest roentgenogram after the removal of pleural fluid showed atelectasis of the left lower lobe. Bronchoscopy disclosed a symmetric, constrictive process beginning above the superior dorsal orifice which appeared to be extra-mucosal, firm, dull-gray and bled a little with instrumentation. Biopsy disclosed only atypical fibrosis. Laminagrams through the left hilar area showed complete obstruction of the lower lobe bronchus, the end of the air column appearing smooth and tapered, suggesting extrinsic pressure. After two weeks of supportive therapy, the patient was discharged improved, nitrogen mustard and radiation therapy being withheld. Some two weeks later, re-admission was again necessary for cough and dyspnea and a repeat bronchoscopy was done with the same gross and microscopic findings as previously observed. Thoracentesis of the left chest yielded 2 liters of fluid and considerably relieved the dyspnea. On November 23, radiation therapy was started to the left mediastinum through anterior and posterior fields. Over a period of four weeks, 2,050 r was delivered. For a period of two months following the completion of therapy, the patient did well after which dyspnea again supervened and was not alleviated by a left thoracentesis. Over an interval covering the next eleven months, 6 additional hospitalizations were necessary for chronic productive cough, progressive dyspnea and recurrent left pleural effusion. Thoracentesis was necessary during each admission and, in addition, 30 mg. of nitrogen mustard was instilled into the left pleural cavity on August 6, 1957 and 20 mg. was given intravenously on September 23, 1957. Two bronchoscopies as well as bronchography (Fig. 2) were performed during this period but yielded no additional information.

The final admission was on April 18, 1958, at which time the patient was seen in the out-patient division and was obviously terminal. She expired the following day.

Postmortem examination disclosed a perforated prepyloric ulcer with acute peritonitis. There was generalized lymphadenopathy as well as foci of tumor in the liver and spleen. The entire left lung was completely atelectatic and bilateral pleural effusion was present. The left mainstem bronchus was infiltrated by scattered zones of tumor tissue. The upper lobe orifice was

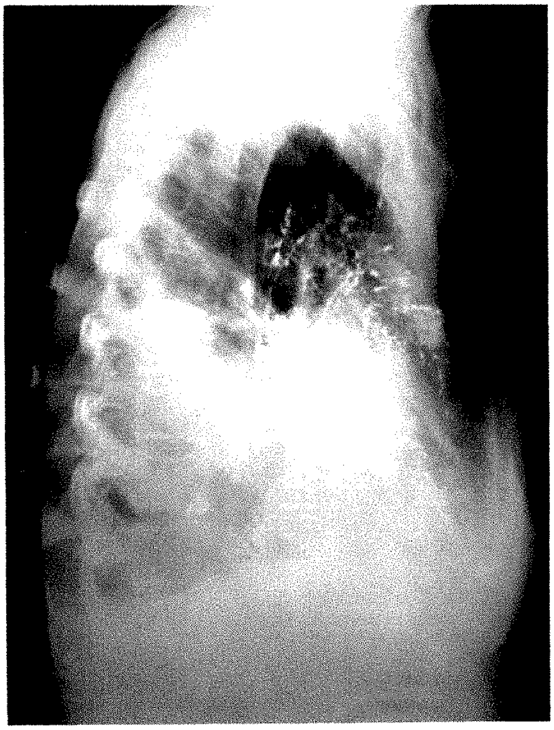

Fig. 2. Case iii. Endobronchial Hodgkin's disease. Bronchogram demonstrating complete obstruction of left lower lobe bronchus with peripheral atelectasis.

very small and the lingular divisions were closed by dense grayish-white desmoplastic tumor tissue. The lower lobe bronchus was patent but showed tumor infiltration in the peribronchial zone. It is to be noted that endobronchial disease was first noted in October, 1956, nine years after the positive establishment of Hodgkin's disease, and was manifested by cough, dyspnea and atelectasis of the lower left lobe.

CASE IV. J. V. B., a sixty-five year old white farmer, was referred to the M. D. Anderson Hospital on November 22, 1955, with the chief complaint of hemoptysis of three weeks' duration. A diagnosis of Hodgkin's granuloma was established at another hospital on January 24, 1954. A chest roentgenogram at this time disclosed right hilar and paratracheal masses.

Physical examination revealed an elderly white male. Small firm lymph nodes were palpable in both axillary areas but there was no cervical or inguinal lymphadenopathy and the liver and spleen were not enlarged. Fine moist rales were heard in the right mid-lung field anteriorly and posteriorly.

Chest roentgenograms and laminagrams showed a large thick-walled cavity in the right parahilar area with a zone of solid infiltration inferiorly and medially (Fig. 3*A*). Bronchoscopy disclosed an irregular grayish-white tumor mass beginning just below the spur of the right upper lobe orifice and extending down the bronchus intermedius. The lumen was so narrowed as to not permit passage of the bronchoscope more than a centimeter below the carina. Biopsy disclosed the presence of an atypical round cell infiltrate which was felt to be compatible with malignant lymphoma. On December 13, 1955, radiation therapy was started, pneumoperitoneum having been established the previous day. An estimated dose of 2,100 r was delivered to the cavity area and right bronchus over a thirty-eight day period and hemoptysis was completely controlled (Fig. 3*B*).

Six months later, the patient was re-admitted to the hospital because of weakness and a 35 pound weight loss. Physical examination disclosed no enlarged lymph nodes or hepatosplenomegaly and the chest was clear. A roentgenogram showed only fibrotic scarring in the previously treated area. An osteolytic area was found in the right ilium. Because of intermittent pyrexia with temperature spikes to 102° F., nitrogen mustard, 20 mg. intravenously, was administered and the patient was discharged two weeks later improved. He has been lost to follow-up examinations and is presumed dead.

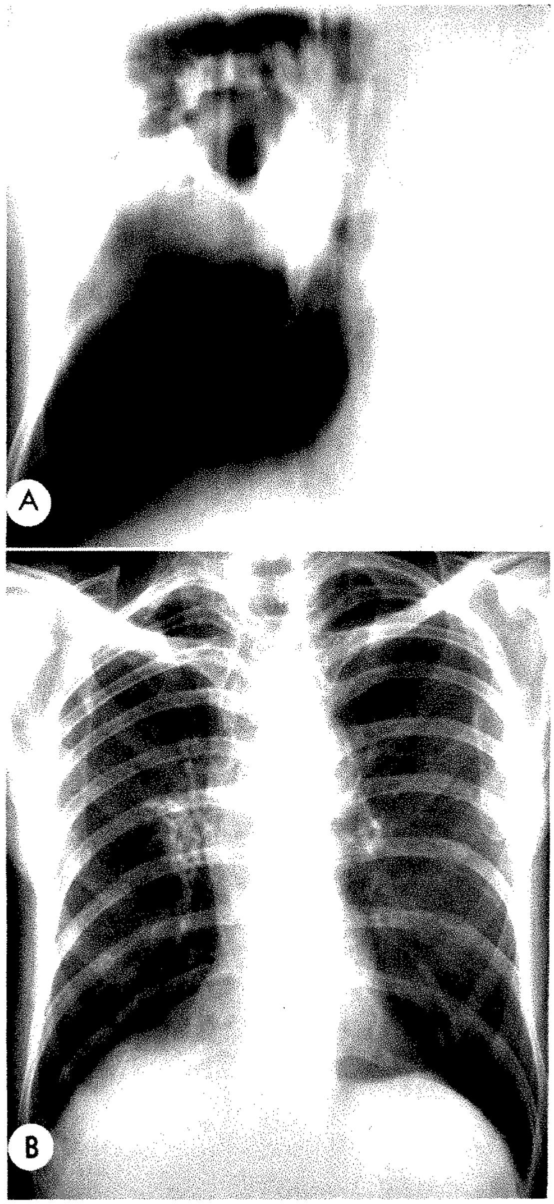

FIG. 3. Case IV. Endobronchial and parenchymal Hodgkin's disease. (*A*) Laminagram showing inflammatory necrosis of parenchymal mass following bronchial obstruction. (*B*) Complete healing with minor residual fibrosis is demonstrated after a course of roentgen therapy.

CASE V. E. Y., twenty-six year old Negro male janitor, was admitted to the M. D. Anderson Hospital on February 19, 1958, with chief complaints of dyspnea, irritating cough

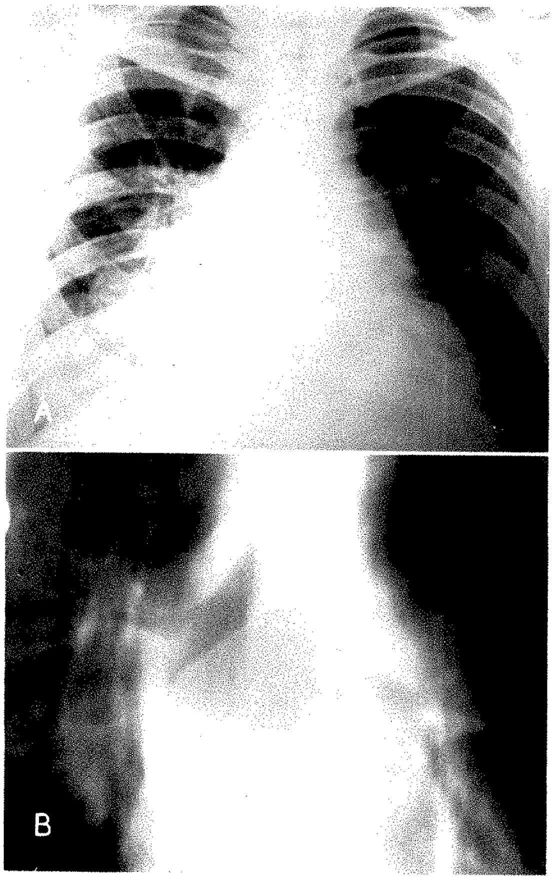

Fig. 4. Case v. Mediastinal, endobronchial and parenchymal lymphosarcoma. (*A*) Conventional chest roentgenogram showing cardiac enlargement and right mediastinal and parenchymal masses. (*B*) Mediastinal laminagram showing conical narrowing of mainstem bronchus below origin of upper lobe division and segmental atelectasis of lower lobe. Extrinsic pressure is evident on left mainstem bronchus.

and wheezing respirations of one week's duration. A diagnosis of lymphosarcoma was established six months previously at another hospital.

A chest roentgenogram showed a right hilar and mediastinal mass with infiltration into the right lung field which was felt to be due to lymphosarcoma. Also, a small right pleural effusion was observed. Thirty milligrams of nitrogen mustard were given intravenously on the second hospital day and the patient was discharged on February 26, 1958, markedly improved with dypsnea virtually absent and cough well controlled. On March 6, 1958, the patient was re-admitted complaining of dyspnea and a dry persistent cough of several days' duration. Breath sounds were distant over the right lung field and expiratory wheezes and ronchi were scattered throughout both lung fields.

A conventional chest roentgenogram (Fig. 4*A*) showed a large mediastinal mass and an intrapulmonary mass on the right side. Laminagrams of the right chest showed a sharp conical narrowing of the right mainstem bronchus immediately below the upper lobe division with segmental atelectasis of the lower lobe (Fig. 4*B*). Gross cardiac enlargement was also present. On the fifth hospital day, bronchoscopy was accomplished under local anesthesia and the bronchus intermedius was noted to be about 75 per cent occluded by a grayish-white nodular tumor mass. Biopsy showed the presence of a round cell infiltrate which was thought to be compatible with the original diagnosis of lymphosarcoma. Sputum cytology examinations were highly suspicious for bronchogenic carcinoma.

On March 24, radiation therapy was instituted to the mediastinum using a grid technique in the 250 kv. range. One week later, marked improvement was noted in breathing and oxygen was discontinued. Therapy was continued until April 24, at which time a tumor dose of 2,400 r was delivered to the mediastinum. At this time, further therapy was withheld because of recurrent dyspnea with increasing edema of the neck, face and upper extremities. Angiocardiography was performed and this revealed complete occlusion of the superior vena cava. This was regarded as secondary to thrombosis rather than tumor and so anticoagulant therapy was instituted; however, the patient continued to worsen and expired on May 9, 1958.

Postmortem examination showed thrombotic occlusion of the superior vena cava with tumor invading its wall, extensive mediastinal lymphoma with invasion of the heart and complete patency of the right and left mainstem bronchi. Histologic examination of the right mainstem bronchus showed a patchy infiltrate of lymphosarcoma tumor tissue with prominent foci of necrosis. The character of the tumor tissue of the mediastinal lymph nodes as well as of the wall of the superior vena cava was that of lymphosarcoma, lymphocytic type, while that of the heart was reticulum cell sarcoma.

DISCUSSION

The clinical picture of endobronchial malignant lymphoma is suggested by a dry, irritating cough, frequently quite severe and associated with dyspnea, in a patient with an established diagnosis of lymphoma. This was noted in 4 of the 5 cases presented. Hemoptysis was the initial complaint in the remaining case (Case IV). The roentgen demonstration of atelectasis in such patients usually indicates the diagnosis, although other potential causes of collapse must be excluded by detailed clinical histories. The atelectasis may involve the entire lung or may be lobar or segmental in distribution. Contrary to the usual opinion, detectable mediastinal lymphadenopathy need not be present nor is the pulmonary collapse often related to mechanical pressure by enlarged or matted lymph nodes. In general, endobronchial lymphoma seems to be a separate manifestation of pulmonary Hodgkin's disease, although in some instances direct spread from adjacent involved lymph nodes may play a part in the production of the atelectasis. However, it should be borne in mind that the range of roentgen findings may be quite diversified as evidenced by the demonstration in separate cases in this series of a parahilar cavity and a mediastinal mass with pulmonary infiltration.

The preferred treatment of endobronchial lymphoma is roentgen therapy and it may be used in palliative or definitive fashion, depending on the general condition of the patient, aggressiveness of the disease and the degree of spread. In general, the philosophy of treatment is to deliver an initial dose of sufficient magnitude so that it will not be necessary to re-treat the same area at a later date. Since the amount of irradiation necessary to open a bronchus and partially clear it of tumor is not very great, the expectant survival of the patient becomes the foremost consideration in deciding dosage. The tumor dosage necessary to sterilize an area of lymphomatous nodes is open to some debate. In general, it may be stated that the tendency is toward higher values in recent years. At the M. D. Anderson Hospital and Tumor Institute, it is felt that a tumor dose of 3,000 r in three to five weeks with an additional 1,000 to 1,500 r to residual masses, when necessary, is required to achieve sterilization. Doses of this magnitude, when delivered initially, seldom result in recurrence in the treated area. Cases I and III had received radiation therapy for mediastinal lymphadenopathy prior to developing endobronchial disease and the doses administered fell short of this arbitrary minimum. Hence, these cases are considered treatment failures in that it is felt that recurrence of the mediastinal disease with the endobronchial complication might have been prevented. In Cases II, IV and V, the presenting pulmonary picture was dominated clinically by the endobronchial deposits and the disease in each of these instances was virulent and aggressive. In these particular situations, the initial radiation therapy should not be considered definitive since the prognosis for life beyond nine months to one year is poor. A tumor dose of 2,000 to 2,400 r in thirty-six to thirty-eight days has been found quite adequate to open the bronchus and control pulmonary symptoms. It must be emphasized that these patients are quite ill, daily tolerance to roentgen therapy is variable and general supportive measures (oxygen, fluids, blood, frequent suctioning) are necessary if the patient is to survive the treatment.

Case III deserves special mention because of the long survival (ten and one-half years) coupled with the unusual response to therapy. Over a three and one-half year period, 4 courses of nitrogen mustard and 2 courses of mediastinal irradiation were undertaken and the response to chemotherapy proved slightly superior than to roentgen therapy. The first remissions induced by nitrogen mustard lasted a total of nine months and objective diminution of mediastinal lymphadenopathy was noted each time. The remaining 2 courses of

nitrogen mustard gave only a transitory benefit lasting a few weeks. The courses of mediastinal irradiation controlled symptoms for a total of four months, but produced no objective changes in the chest roentgenogram. This is the opposite of the expected therapeutic result in that irradiation is usually the superior modality for the control of focal manifestations of lymphoma.

These 5 cases, constituting examples of bulky intraluminal growth or bronchostenosis, are but one type of endobronchial involvement in malignant lymphoma. The more common form is a granulomatous panbronchitis or peribronchitis which may be associated with a granulomatous interstitial pneumonia.[5] Attention is not called to the involvement of the respiratory passages in this form since the bronchi become part of the disease process "without ever having the lead."[1] In the remaining type, scattered plaques and nodules are the primary manifestations and are usually multiple and diffuse. Heretofore, this has been a postmortem finding except when the nodules become sufficiently large to produce obstructive symptoms.

SUMMARY AND CONCLUSIONS

1. Four cases of malignant lymphoma presenting as mass endobronchial lesions and one presenting as bronchostenosis are described.

2. The complication is characterized by persistent, dry, irritating cough, usually associated with dyspnea and the physical and roentgen findings of atelectasis. The roentgen picture does not differ in any way from that of atelectasis due to other causes; however, it has not been widely emphasized that endobronchial disease is usually responsible for the atelectasis and that pressure from enlarged mediastinal lymph nodes does not play a singificant part in the bronchial occlusion.

3. Bronchoscopy revealed obstructive nodular lesions in 4 cases and an extramucosal constriction in the remaining case. Bronchoscopic biopsy was definitive in 1 case only.

4. Criteria for adequate roentgen therapy are postulated and it is urged that such treatment be given initially to uncomplicated mediastinal lymphadenopathy. Failure to do so may result in recurrence of the disease in the treated area with complicating endobronchial involvement. This was believed to have occurred in 2 of the presented cases.

5. Endobronchial involvement dominated the initial pulmonary manifestations in 3 instances. This is probably indicative of virulent disease and the prognosis of survival beyond nine months to one year is poor. Therapy in palliative doses is usually adequate to control obstructive pulmonary manifestations in such cases.

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ADDENDUM

Since the submission of this report 2 additional patients with endobronchial invasion have come to our attention.

The first of these, a sixty-one year old white female, complained of a spastic, irritating, nonproductive cough with increasing dyspnea of three months' duration. Lymphosarcoma had been previously diagnosed from a left cervical lymph node biopsy on July 1, 1952. Physical examination disclosed very distant breath sounds in the left lung field and the chest roentgenogram showed bilateral emphysema which was increased as compared to previous examinations dating back several years. Bronchoscopy disclosed a lymphomatous occlusion of the left mainstem bronchus at the level of the carina. Bronchoscopic secretion was classified as malignant cells, Grade V, and the biopsy as reticulum cell sarcoma. Nitrogen mustard, 20 mg. intravenously, has presently controlled respiratory symptoms and radiation therapy is to be administered.

The second patient, brought to our attention through the courtesy of Dr. Leonard C. Doubleday, was a fifty year old white female with the

chief complaint of pain in the chest. A conventional roentgenogram of the chest disclosed a small quantity of fluid on the left in association with atelectasis of the left lower lobe. In the lateral projection, a small anterior mediastinal mass was demonstrable. Bronchoscopic studies showed a tumor of the left lower lobe bronchus which was interpreted by the pathologist as undifferentiated squamous cell carcinoma. Irradiation was administered and, after a tumor dose of 1,000 r, complete re-expansion of the left lung was obtained and therapy was discontinued. The patient was relatively well for approximately one year at which time mediastinal adenopathy recurred as well as skeletal disease. The patient went downhill rapidly and expired from systemic lymphosarcoma. Review of the original slides indicated that lymphomatous tissue had been responsible for obstruction of the left mainstem bronchus.

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ROENTGEN THERAPY IN WEGENER'S GRANULOMATOSIS*

A CASE REPORT

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WEGENER'S granulomatosis is a rare disease of undetermined etiology characterized by (a) granulomatous ulcerative lesions in the upper respiratory tract, (b) widespread granulomata, seen frequently in the lung, kidney, and spleen, and (c) widespread vasculitis and glomerulitis. The onset is insidious, beginning with nasal obstruction, crusting, epistaxis, or antral pain, or lower respiratory tract symptoms such as cough, pleurisy, or hemoptysis. The disease occurs most often in young or middle aged adults and runs a course averaging five months until death. The longest survival has been reported as four years.[13] Death is usually caused by renal involvement.

Some aspects of the condition closely resemble malignant granuloma of the nose,[1,4,5,11,12,14] whereas others appear more like periarteritis nodosa.[12,13] No bacterial or viral agent has been implicated. Most authors infer that an immunologic reaction must be considered as the cause of the disease,[2,7,8] but the evidence is not conclusive.

In treating these patients, antibiotics and steroids have been used. Radiation therapy has produced a temporary response in malignant granuloma of the nose,[4,6,9,11,12] but has been used in only a limited number of cases of Wegener's granulomatosis. In these instances, however, irradiation produced at least temporary regression of the lesion.[4,5] Walton,[13] in a recent concise review of the subject, held the belief that the treatment of choice in Wegener's granulomatosis is radiation therapy to the local lesion, together with suitable antibiotics to control secondary infection. He stated that steroids should be withheld until the local lesion has healed so that defense against infection of the open lesions is not hindered. Some authors,[2,7,10] on the other hand, make no mention of radiation therapy.

In the patient reported here, roentgen therapy produced good temporary regression of local lesions, but the ultimate outcome was, as usual, death.

REPORT OF A CASE

The patient was a forty-four year old white housewife who was first seen in the Radiation Therapy Department of the University of California Medical Center in April, 1958, with a two months' history of painless swelling in the right parotid gland region. Occasional warmth of the skin overlying the mass had been noted, but there had been no real pain or tenderness. Sialography had been reported as negative. The swelling did not appear to be the usual parotitis. A biopsy was not done.

After the mass had enlarged slightly during a period of two months, and had been diagnosed as chronic parotitis, roentgen therapy to a dose of 1,100 r in air (1,300 r on skin) was delivered in fifteen days using 250 kv. peak, Thoraeus III filter, half value layer of 3.2 mm. Cu and target skin distance of 50 cm. The size of the mass decreased during treatment and it was no longer detectable two months later.

When seen in August, 1958, the patient had • been hoarse for three weeks and had some edema in the left side of the larynx, asymmetry of the neck, and generalized swelling of the right temporalis muscle. During that time she had developed a fever, enlarged bilateral submandibular lymph nodes, and purulent exudate in the pharynx. She was admitted to the hospital and an enlarged submental lymph node was removed for biopsy, since the possibility of a lymphoma was being considered. The pathologist reported "marked hyperplasia of lymph node showing focal necrosis and eosinophilic infiltration." Ulcerations appeared on the hard palate and large masses in the tonsillar regions were covered with exudate. Histologic examination of hypertrophied oropharyngeal lymphoid

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bands showed a granulomatous process of "unclassified" type, with ulceration. The blood cell count, chest roentgenogram, urinalysis, and bone marrow tests were normal. With nonspecific supportive care, her general condition improved and the patient was discharged after three weeks in the hospital.

She was readmitted on October 6 with a productive cough, fever, elevated white blood cell count, and roentgenographic evidence of patchy pneumonitis at the right lung base. There was edema of the larynx, lymphoid hyperplasia in the posterior pharynx, and white plaques over the posterior pharynx and larynx. A tracheotomy was performed because of respiratory embarrassment. Biopsy of a posterior cervical lymph node revealed "reticulo-endothelial hyperplasia" and a subsequent biopsy of the hypopharynx was reported "chronic nonspecific granulomatous ulcerative inflammation." Treatment consisted primarily of penicillin and prednisone. The laryngeal edema decreased, pneumonitis subsided, and the tracheotomy tube was removed. She was discharged on prednisone after a hospital stay of seven weeks.

On January 4, 1959, the patient was readmitted because of fever and inability to swallow. At that time, she had granulomatous lesions of the lateral pharnyx with general mucosal hypertrophy and superficial ulceration of the aryepiglottic folds. Since the original therapy to the parotid area had led to marked regression, roentgen therapy was given to both sides of the neck, using the same factors as in the previous treatment of the parotid area, delivering 400 r in air (500 r skin dose) to each side in ten days. The symptoms were relieved temporarily and the pharyngeal and laryngeal edema was greatly reduced. Ten days later, however, there was increased edema in the submental and submandibular areas, with recurrent difficulty in breathing and swallowing. Roentgen therapy of 600 r skin dose in six days was given to the submental area, which resulted in amelioration of symptoms and in regression of the swelling. At this time, nodular densities in the lower lung fields were noted in roentgenograms and reported as "consistent with Wegener's granulomatosis."[3] Although the densities increased, the patient's fever and symptoms subsided and she was discharged on February 2, 1959.

On March 14, 1959, the patient was readmitted because of high fever, weakness, dyspnea, and swelling of the neck tissues. Her pharynx was again injected, with slight hypertrophy of lymphoid tissues. A sinus tract had developed from the left pyriform sinus into the soft tissues of the neck and was demonstrated, by contrast roentgenography to extend to the level of T1 (Fig. 1). Roentgenograms of the chest showed multiple nodular densities in the lungs, one with cavitation (Fig. 2). A new biopsy of the pharyngoesophageal area showed "non-specific chronically inflamed granulation tissue." Edema of the tissues surrounding the trachea caused marked narrowing of the airway down to the level of the coryna. Treatment was continued with prednisone and antibiotics. During the last three days of life, the patient received roentgen therapy to the neck and superior mediastinum, 100 r skin dose daily, but she died of respiratory obstruction on April 3, 1959.

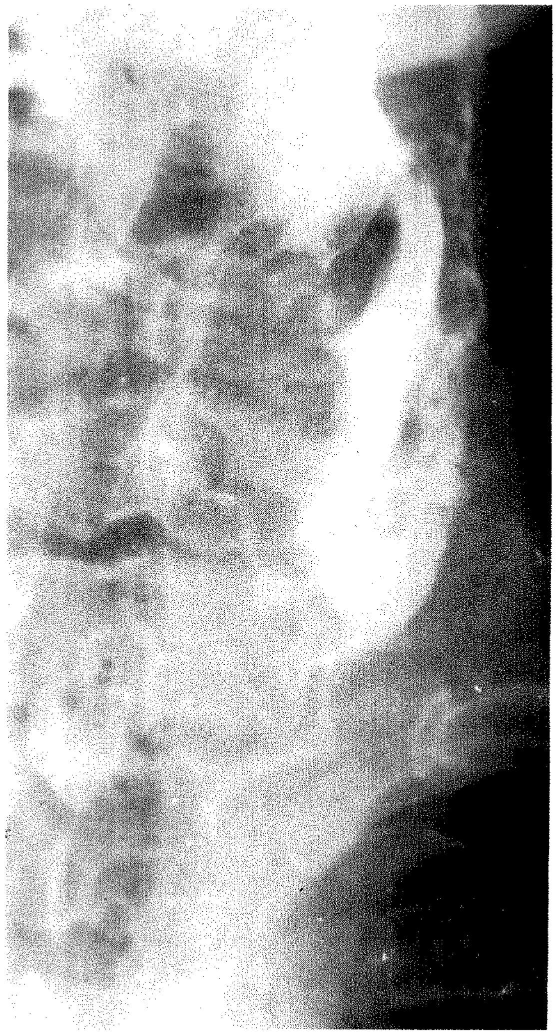

FIG. 1. Contrast medium outlines a fistulous tract from the left pyriform sinus to the level of T1.

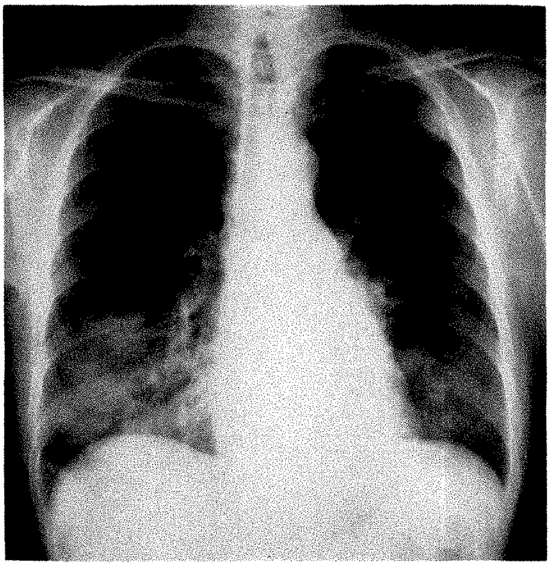

FIG. 2. Chest roentgenogram, at the time of final hospital admission, shows mutliple nodular densities in both lungs with cavitation near the right hilus. In addition, there is some consolidation in the right middle lobe. Note the narrow airway in the larynx.

Postmortem examination showed granulomatous lesions in the nasopharynx, hypopharynx, larynx, and trachea. The epicardium showed profuse infiltration with round cells, eosinophils, and the suggestion of a pseudogranulomatous pattern in focal areas. In the mediastinum, a granulomatous reaction involved the great vessels and the roots of the lungs, with a gross residual alveolar pattern in the background, and eosinophilic, necrotic, hyalinized material. Peribronchial infiltration with round cells gradually changing to eosinophilic infiltration, central necrosis, and epithelioid cells, and panperivascular infiltration of arteries and veins were seen. The parotid glands appeared normal except for postmortem autolysis and periductal fibrosis. The kidneys showed occasional focal round cell infiltration in the perivascular areas, and glomerular tufts showed adhesions to Bowman's capsule, some engorgement and edema, and round cell infiltration. The final diagnosis was Wegener's granulomatosis.

SUMMARY

Wegener's granulomatosis, a fatal disease of questionable etiology, produces granulomatous, ulcerative lesions in the upper respiratory tract, widespread granulomata, and widespread vasculitis with glomerulitis. Treatment with antibiotics, steroids, and roentgen therapy produces temporary palliation only.

A patient is reported in whom roentgen therapy produced dramatic, although only temporary, relief from upper respiratory lesions, supporting Walton's statement that radiation therapy is of value in treating the local lesions of this disease.

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THE EARLY DIAGNOSIS OF PROSTATIC MALIGNANCY BY THE USE OF P^{32}*

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Carcinoma of the prostate is the most frequent of the malignant neoplasms found in men over fifty years of age, and the third in incidence as a cause of death. The early diagnosis of this malignant tumor, while the process is still confined to the gland and curable, is extremely difficult at the present time. The most common screening procedure used is the digital examination, which is unreliable in early carcinomas. In one reported series, only 23 per cent of early malignant tumors were correctly diagnosed by palpation.[3] Jewett[4] compared the digital rectal examination findings in 108 benign and 103 malignant nodules of the prostate and was unable to find any discernible difference.

Tissue examination is, of course, the ideal method of diagnosis. However, tissue obtained by transurethral resection is unreliable for diagnostic purposes because this procedure does not always remove tissue from the posterior lobe—the most frequent area of involvement. Perineal needle biopsy is a more satisfactory method but is a blind procedure. The area of involvement, especially if small, may be readily missed. Biopsy through the rectum is an operating room procedure requiring anesthesia. While the results are satisfactory, the morbidity is somewhat high. Open perineal biopsy is the best method. It is, however, a major operative procedure.

The necessity for additional diagnostic methods to supplement the digital examination, yet not requiring surgery, becomes apparent.

We have, therefore, tried to develop a quick, simple, and reliable screening test which will aid in determining when more definitive diagnostic measures are needed. The test is based on the differential absorption of radioactive phosphorus (P^{32}) by benign and malignant tissue. These differences in absorption are measured by a small Geiger-Müller probe which is inserted into the rectum over the area of the prostate.

BIOLOGIC BACKGROUND

P^{32} is a pile-produced isotope with a half life of 14.3 days. It is a pure beta emitter with the beta particles having a maximum energy of 1.7 mev.

Marshak,[7] in 1940, found high concentrations of P^{32} in tumor nuclei of mice lymphoma transplants. He concluded that the greater uptake in the tumor cells was due to their increased mitotic activity and was not a specific characteristic of this tumor.[7]

Others have shown that the higher pickup of P^{32} was due to its intracellular incorporation into desoxyribonucleic acid, ribonucleic acid and other nucleotides which are present in higher concentrations in malignant cells. This was demonstrated in such tumors as those of the ovary, breast, stomach, and prostate.[6,9,10,11] Along with the increased formation of nucleic acids, their metabolic activity has been shown to be higher by increased P^{32} turnover. Schulman *et al.*[11] demonstrated that the increased rate of P^{32} turnover was limited to the cancer cells themselves, and that these changes were not demonstrable in the surrounding tissue.

In 1941, Kenney *et al.*[5] introduced the concept of the "differential absorption ratio" (D.A.R.). This is the ratio of P^{32} absorbed by the tissue in question in relation to the amount the tissue would have

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contained if the isotope had been equally distributed throughout the body. He was able to show significant differential absorption ratios in breast adenocarcinoma, osteogenic sarcoma, and lymphosarcoma.

Inflammatory tissue has also been shown to absorb P^{32} in different amounts than malignant tissue. Thomas *et al.*[14] induced inflammatory lesions in the eyes of rabbits and found that after an initial increase in absorption, due to the increased vascularity associated with inflammation, the uptake gradually approached that of the normal eye over a period of minutes. For this reason it was felt that there would be no difficulty in differentiating inflammatory from malignant lesions. Low-Beer[6] was able to demonstrate differences between breast carcinomas and mastitis.

Histologic differences in cells do not affect the counting rate. The concentration of the isotope within the cell is reflected by the count rate, which is dependent upon physiologic changes and biochemical activities of the cell, not upon morphologic characteristics.[9]

CLINICAL BACKGROUND

Selverstone *et al.*[12] used P^{32} for localization of brain tumors, inserting a specially designed Geiger-Müller probe into the brain substance.

Low-Beer[6] was the first to apply external scanning to the breast. Because of the limited range of P^{32} beta rays in tissue, this method is limited to lesions greater than 3 to 4 mm. in diameter and no deeper than 5 to 6 mm. from the surface. In his first report of 197 patients he used the criterion of a pickup greater than 25 per cent over that of normal tissue as indicative of malignancy. In this series he had but one false positive and three false negative results.[6]

Others have applied similar techniques to eye lesions. Many feel that this test will probably find a useful place in ophthalmology.[15] There are, however, limitations to the study in this area, *e.g.*, movements of the patient's eyes, errors in technique and the short range of the P^{32} beta rays.[1] Because of this, a negative test here does not exclude malignancy; however, a positive one is strongly suggestive of it.[1]

METHOD

Twenty-nine consecutive patients admitted to the genitourinary ward who were to have various procedures necessitating biopsies or sections of the prostate gland were selected. All were over forty years of age. A dose schedule of 5 μc of P^{32} per kilogram of body weight was used. It was given intravenously to preclude variations in absorption. The dosage employed here is comparable to that in previously reported studies on eye and breast lesions. A Selverstone-type brain probe attached to a count rate meter was used.

The prostate gland was divided for recording purposes into four quadrants. The patient was examined as in any routine rectal examination. The probe was then introduced along the finger and each quadrant of the gland was scanned separately. The readings which were recorded were those taken in that part of each quadrant with the highest count rate. Additional readings were taken over any suspicious nodule. The count was recorded only when the rate meter gave a constant reading of double the time constant selected. In our series, 20 seconds was used.

DISCUSSION

This experiment was set up to determine whether malignant areas of the prostate would pick up significantly greater amounts of P^{32} than normal tissue, and whether this difference could be detected by external counting.

Normal tissue must be present in the prostate gland for this test to be valid, since there can be no absolute values to indicate malignancy. The normal prostatic tissue of the individual thus serves as his own control.

The results of the study are given in Table I. The microscopic report confirmed the scanning interpretation in every case.

Count rates of greater than 50 per cent

Table I

RESULTS OF SCANNING FOR P^{32} UPTAKE

Patient	Right Upper Quadrant	Right Lower Quadrant	Left Upper Quadrant	Left Lower Quadrant	Impression from P^{32} Study	Clinical Impression	Pathologic Diagnosis
1	500	600	500	600	B	B	B
2	900	800	800	700	B	B	B
3	300	240	460	(600)	M	M	M
4	320	380	(480)	(500)	M	M	M
5	240	300	320	(480)	M	M	M
6	680	740	820	680	B	B	B
7	(600)	300	240	200	M	M	M
8	400	500	510	520	B	B	B
9	220	240	280	300	B	M	B
10	220	200	260	250	B	B	B
11	450	400	420	400	B	M	B
12	140	140	130	150	B	B	B
13	160	170	140	160	B	B	B
14	(540)	380	300	280	M	M	M
15	440	420	380	400	B	B	B
16	200	220	180	160	B	B	B
17	400	380	370	300	B	B	B
18	200	200	180	240	B	B	M
19	240	(380)	300	280	M	M	M
20	230	160	(360)	230	M	M	M
21	320	240	(420)	300	M	M	M
22	380	380	400	380	B	B	B
23	200	200	180	150	B	B	B
24	280	280	280	260	B	B	B
25	220	280	280	250	B	B	B
26	180	200	220	200	B	B	B
27	340	260	260	300	B	B	B
28	320	320	240	300	B	B	B
29	360	320	320	380	B	B	B

Note: All numbers under various quadrants are in counts per minute.
Parentheses about a number indicate a significant count rate.
B = Benign.
M = Malignant.

SUMMATION OF RESULTS

	Impression from P^{32} Study	Clinical Impression	Pathologic Diagnosis
Malignant	8	10	9
Benign	21	19	20
Total	29	29	29

over supposedly normal tissue were considered indicative of malignancy. The data were then broken down into two groups on this basis—one designated "malignant" and the other "benign."

A chi-square test was performed which showed that the differences in our diagnosis from those found at microscopy may be attributed to chance variations in our readings. No significant difference between the two could be found (Table II).

An *analysis* of the *variance* was under-

Table II

CHI-SQUARE X^2

	P^{32} Test Results (Po)	Pathology (P)
Benign	21	20
Malignant	8	9

$$X^2 = \sum \frac{(Po-P)^2}{P} = \frac{(21-20)^2}{20} + \frac{(8-9)^2}{9} = .16$$

Note: .16 is not significant.

taken to isolate the factor of individual patient differences in counting rates. The intrinsic variability of the benign and malignant groups was then compared (Table III).

With the factor of patient variation eliminated we would expect that if there were no other factors present except experimental error (variations of equipment, differences in reading of the counts, etc.) there would be no significant difference between the two groups. However, the intrinsic variability of the malignant group was six times that of the benign group. This fact precludes the difference between the two groups as being due to chance. There must, therefore, be another factor present causing this variability, namely, the presence of cancer in part of the gland.

If there is no normal tissue present, a differential absorption cannot be obtained and malignancy cannot be diagnosed by this means. This supposition was tested in several patients with known diffuse involvement of the prostate. As was expected, counts were uniform throughout the gland and no diagnosis could be made by our technique.

Nodules are ideal for evaluation by this method. Two patients in our series had nodules which were clinically believed to be malignant. P^{32} uptake studies failed to show any differential pickup and our impression was confirmed by biopsy, which showed these nodules to be benign.

The time at which the procedure was performed was not found to be critical. The patients were initially examined over varying time intervals ranging from 10 minutes after injection to over a week. The highest readings were obtained in the 10 to 20 minute intervals, probably due to the high concentration of the isotope in the vascular

Table III

ANALYSIS OF VARIANCE

	Sum of Squares	df
Total Variability	$\sum X^2 - \frac{(\sum X)^2}{N}$	$N-1$
Variability between Men	$\frac{(\sum X_m)^2}{n_r} - \frac{(\sum X)^2}{N}$	$n_m - 1$

X = each individual value.
N = total number of observations.
n_r = number of readings for each man.
n_m = number of men.

$$\text{Experimental Error } \Sigma X^2 - \frac{(\Sigma Xm)^2}{n_r \quad N - n_m}$$

MEN CONSIDERED AS HAVING CANCER

	Sum of Square	df	Mean Square Variance
Total Variability	4,754	31	
Variability between Men	2,766	7	395
Experimental Error	1,988	24	82.8

The intrinsic variability of the cancerous men is $T_c^2 = 82.8$
$T_c = 9.1$

MEN CONSIDERED AS HAVING BENIGN PROSTATE

	Sum of Square	df	Mean Square
Total Variability	26,264	83	
Variability between Men	25,374	20	1,269
Experimental Error	890	63	14.13

$T_B^2 = 14.13$ or $T_B = 3.7$

Utilizing the "F" test to determine whether the difference between the two variants is due to chance,

$$F = \frac{Tc^2}{T_B^2} = \frac{82.8}{14.1} = 5.9$$

This result is highly significant even at the 1 per cent level.
Note: all basic values have been divided by 10.

bed of the prostate and the immediate surrounding areas.

In our study we found that the most reproducible and most reliable results were obtained in the 24 to 48 hour period, since variability of blood supply to the gland was eliminated. Count rates could also be successively duplicated with greater accuracy during this period. This was also the interval in which the greatest differentiation between benign and malignant areas was obtained. The examination can be performed at one's convenience any time during the 24 to 48 hour period since counts do not appreciably vary during this span of time.

There are two major limiting factors to this study. First, the test is inherently limited by the range of the P^{32} beta rays in tissue. If the lesion is not within 5 to 6 mm. of the examining finger it will not be detected by the probe. The second main difficulty can be attributed to the design of the probe used in this series. The Selverstone-type probe which was used can lead to three different sources of error: (1) Because of its low sensitivity there will be low count rates which can lead to statistical inaccuracies. (2) The tip is bulbous and is sensitive throughout its entire surface. This factor, before it was discovered, led to erroneously high readings in the upper quadrants of the prostate gland in patients with large hypertrophied glands. In these cases, the finger was removed from the probe tip in an attempt to get the probe in the upper part of the gland. With removal of the finger, the probe received impulses not only from the prostate gland but from the surrounding rectal mucosa. This can lead to false positives and must be guarded against. (3) Since the tip is bulbous, differences in finger pressure result in varying amounts of the surface indenting the gland, thus changing the counting area. This theoretically can lead to changes in count rate.

It is felt that the technical difficulties can be overcome with a properly designed probe. Such a probe would consist of a pancake-type tip, sensitive in only one plane and having a high sensitivity in the beta range of P^{32}. A flexible stem would also be desirable. With such a probe, the accuracy and reliability of this test should be greatly enhanced.

SUMMARY

A new approach to the diagnosis of early prostatic malignant neoplasms using radioactive phosphorus is described. The technical limitations of the study and the equipment used are described. Technical improvements in the equipment are suggested. Although further experience with this test is needed, we feel that it is potentially an accurate, simple, and reliable diagnostic aid which should prove valuable in detecting early prostatic malignant tumors.

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USE OF A Cs^{137} STANDARD OF SPECIAL DESIGN TO CALIBRATE SCINTILLATION SPECTROMETERS FOR CLINICAL I^{131} MEASUREMENT*

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THE adoption of gamma-ray spectrometry techniques to eliminate scattered and background radiation in clinical I^{131} measurements has become widespread.[1-4] The complexity of the required equipment has introduced the major problem of assessing the reliability of results obtained by personnel who usually have a superficial knowledge of electronics and nuclear physics. The physician can only have complete confidence in the measurements if a simple and reliable method of calibration is adopted. It is especially desirable that this calibration be quantitative enough that a percentage deviation in the calibration reading correlates with the same percentage deviation in the sample when the deviations are instrumental.

In the Radioisotope Service Clinic of the Houston Veterans Administration Hospital, we have worked out a procedure for calibration which satisfies this requirement. The procedure involves simple switching between a specially prepared long-lived Cs^{137} standard and the I^{131} sample. The simplicity of switching is a major feature of the method, since there must be no possibility of interjecting uncorrelated deviations in sample and standard by introducing the judgment of the operator in setting pulse-height-analyzer biases, amplifier gain, etc., between readings. The second major feature of the method is the introduction of scatter broadening into the Cs^{137} gamma ray spectrum by embedding the source in an aluminum scattering cylinder. It is this feature that allows quantitative comparison between deviations of sample and standard. The thirty year Cs^{137} with a single gamma ray has proved a more effective standard than "mock iodine"[2] using Ba^{133}.

The calibration procedure has been in use for over two years. Consistency of measurement within two per cent has been achieved on I^{131} samples in which activities have been accurately determined by established assay procedures.

METHOD

Amplifier Pulse-Voltage Divider. Since Cs^{137} and I^{131} emit respectively 660 kev. and 360 kev. gamma rays, a two position voltage divider is used at the output of the linear amplifier. In one position the total pulse voltage output of the amplifier is delivered to the pulse height analyzer. In the other a factor 360/660 is introduced so that the 660 kev. gamma ray can be analyzed in the same channel as the 360 kev. gamma ray. This is done with a single switch on the operator's panel, one position being used for I^{131} measurements and the other for Cs^{137}. Unquestionably, there are many ways to make a pulse voltage divider. We have used a tap on the cathode resistor of the cathode follower at the amplifier output. This method proved simple and effective.

The circuit is shown in Figure 1. On position 1 of the switch, the analyzer receives the pulse voltage developed by the cathode follower; on position 2 it receives a fraction approximately equal to $r_2/(r_2+r_1)$ of the pulse voltage. Due to stray capacitance and the finite input impedance of the analyzer, the ratio $r_2/(r_2+r_1)$ cannot be made exactly equal to the ratio 360/660. Final resistor values must be found by trial and error after observing the pulse spectra of Cs^{137} and I^{131} at the two switch positions.

In equipment where the amplifier output cathode follower was part of an in-

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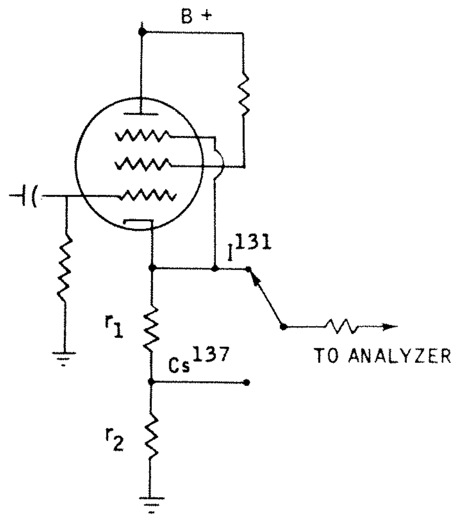

FIG. 1. Diagram of voltage divider system.

verse feedback loop, it was necessary to insert an additional cathode follower as a voltage divider in order not to disturb the feedback. Since this tube drew only a few milliamperes, the addition was not deleterious.

A minor unsolved problem in our equipment lies in the need to modify the ratio $r_2/(r_1+r_2)$ slightly when photomultiplier tubes are replaced. Since replacements have been necessary only after one or two years of use, the recalculations and recalibrations have not proved a major inconvenience.

Pulse Height Analyzer Bias Calibration. A small but important part of the calibration procedure is the monitoring and adjusting of the pulse height analyzer biases. Gain and bias are independent system parameters. In evaluation of system performance, it is necessary to know that the biases are correct before the Cs^{137} standard and overall reading can be taken as a measure of gain stability. A simple and inexpensive pulse generator is used to check the pulse height analyzer bias settings whenever there is doubt about system performance or at intervals dictated by experience. Satisfactory generators are available commercially or can be constructed from circuits described in the literature. In equipment where the pulse amplifier and pulse height analyzer were incorporated in a single electronic unit, it was found useful to incorporate a simple pulse generator in that unit.

The Cs^{137} Standard Source. It is not sufficient to bring the 660 kev. gamma ray of the Cs^{137} standard into the pulse height analyzer channel at the settings used to measure I^{131}. It is also necessary that fluctuations in amplifier gain and channel biases produce the same fractional change in count rate for the Cs^{137} standard as for the I^{131} sample. Details of the pulse spectra of the two radioisotopes must be examined to see if this is possible. Figure 2 shows a comparison of typical pulse spectra obtained from a Cs^{137} point source and an I^{131} sample in the usual form of a 30 ml. water solution. The resolution for the Cs^{137} gamma ray was 9.1 per cent; *i.e.*, the full width of the peak at half height was 9.1 per cent of the position of the maximum measured along the pulse height axis. The data

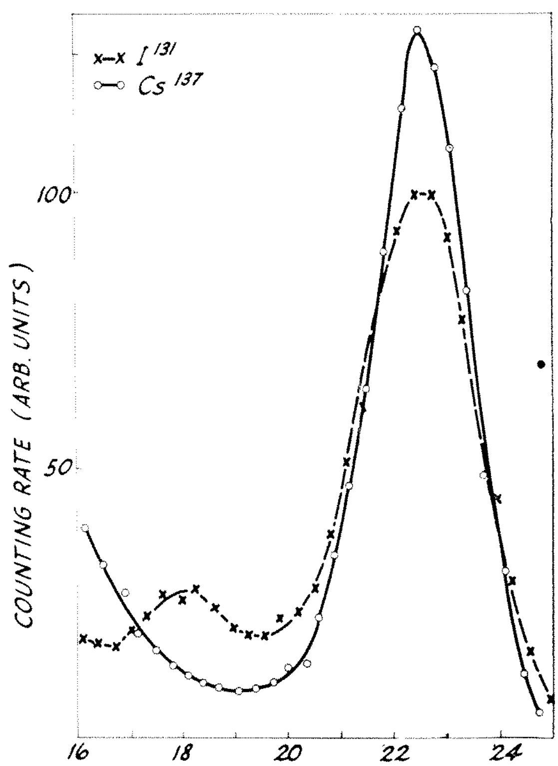

FIG. 2. Pulse spectra of Cs^{137} point source and I^{131} standard source in 30 ml. water.

were taken with half volt channels and a gain such that the peak was at 60 volts, so that the widths of the analyzer channels did not affect the resolution. Abscissas were then reduced to bring the peaks to 22.5 volts, the value used in actual uptake measurement. The peak of Cs^{137} is of course narrower because of photomultiplier statistics.

The ordinates of the spectral curves of Figure 2 are proportional to counts per second per volt pulse height interval. Therefore, the area under a curve between any two points on the pulse height axis is a measure of the contribution to the counting rate from that interval in the spectrum. The curves are normalized to have the same area between 19.0 volts and 26.0 volts pulse height, because in our I^{131} measurements we include the spectrum between 19.0 and 26.0 volts by using a 7 volt channel with the lower bias at 19 volts. The ordinate at 19 volts is approximately equal to gain or loss of counts by a 1 volt downward or upward shift in the lower bias. It is easily seen that the 1 volt shift has a larger effect percentagewise on the I^{131} reading. By actual measurements, the change is 7 per cent for I^{131} as compared to 3 per cent for the Cs^{137} point source. A change in gain which shifts the peaks in the channel likewise has a correspondingly larger effect on the I^{131} reading.

Figure 3 shows a comparison between the same I^{131} spectrum and a Cs^{137} pulse spectrum obtained when the Cs^{137} source is embedded in a 1 inch diameter aluminum rod with $3\frac{1}{2}$ inches of aluminum between source and detector. Again the areas under the curves between 19 and 26 volts are the same. The change in the cesium spectrum from Figure 2 to Figure 3 in the 19 volt region shows the effect of Compton scattering by the aluminum. The cesium spectrum in Figure 3 approximates the I^{131} spectrum at 19 volts fairly well. The spectrum of Figure 3 is that of a standard source actually adopted. If the baseline of a 7 volt channel is actually varied for both I^{131} and this Cs^{137}-in-Al source with all other set-

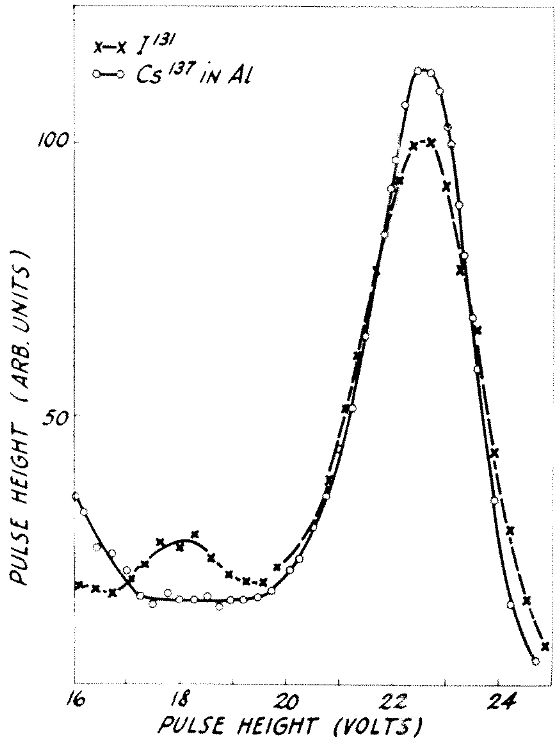

FIG. 3. Pulse spectra of Cs^{137} point source in aluminum scatterer and the I^{131} standard source.

tings as in actual uptake measurements (*i.e.*, both peaks at 22.5 volts on the appropriate selector switch positions, etc.) the counting rates obtained as a function of baseline in the neighborhood of the 19 volt operating point are shown in Figure 4*b*. Figure 4*a* shows the results of gain variation with baseline remaining constant. A satisfactory parallelism between the curves is seen to exist, so that the Cs^{137}-in-Al source of Figure 3 constitutes a satisfactory standard.

Figure 5*a* shows the physical arrangement of the Cs^{137}-in-Al source in use with our detector; Figure 5*b* is the diagram of the cesium standard and detector. The standard is shown in relation to the scintillation crystal, lead shield and locating device of an I^{131} uptake instrument, as it is used in the standardization of that instrument.

The problem of tailoring the Cs^{137} spectrum to the I^{131} spectrum can only be attacked after a choice of operating condi-

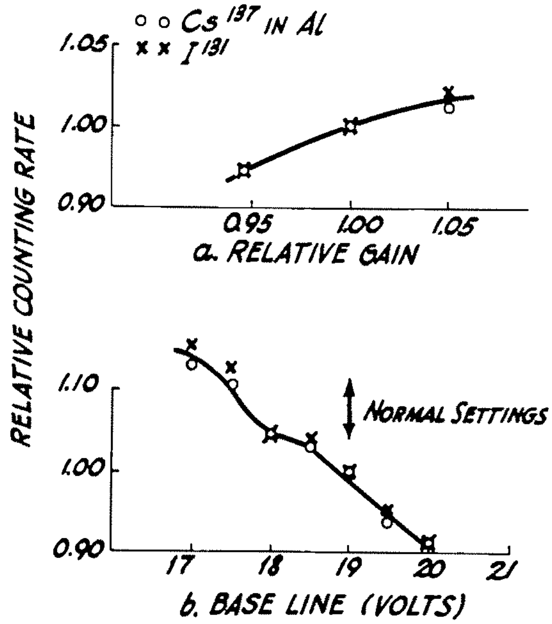

FIG. 4. Relative variations in counting rate. (*a*) Small gain variations with constant normal baseline. (*b*) Small baseline variations with constant normal gain. Standard geometry and 7.0 volt channel width in both cases.

tions is made. The fact that we have chosen the aluminum dimensions to give best correspondence between the spectra at 19.0 volts was governed by the choice of the 19–26 volt interval in the I^{131} spectrum with the peak at 22.5 volts. The choice has some arbitrariness. Considerations of counting rates in relation to I^{131} dosage, stability of counting rates in the face of small gain and bias variations, and in fact the achievable shaping of the Cs^{137} pulse spectrum were all factors in the choice. Some attention will be paid in later sections to this point.

DESIGN OF THE Cs^{137} STANDARD

While many scattering geometries are possible, consideration was limited to cylindrical masses of aluminum with the Cs^{137} source embedded on the cylinder axis. Only cylindrical geometries were considered because success with more complicated shapes appeared to depend too critically on the judgment of the operator in positioning the source under the detector. After preliminary success with several cylinders was achieved, considerable effort was devoted to understanding the relation between the form of the spectrum and the mass and dimensions of scattering material. Calculation appeared more promising than measurement where the pulse distribution was observed with 10 per cent energy resolution at 660 kev. due to photomultiplier statistical broadening. Numerical calculations were made for a number of cylinder sizes. The calculations were checked in the case of several large cylinders where the scatter broadening was measurable with the available resolution. A few of the results are given below to show what may be accomplished.

To estimate the scatter spectrum, single scattering events of the type shown in Figure 6 were considered in the calculations. The source is located at A on the cylinder axis AA'. To reach the detector after being once scattered through angle θ, a photon was assumed to leave the source at angle θ and to be scattered into approximate parallelism with the cylinder axis. The scattered spectrum reaching the detector could be calculated on this approximation in terms of the electron density in the aluminum, the solid angle subtended by the detector, and the differential cross section for Compton scattering per unit solid angle through an angle θ. The differential cross section for Compton scattering and the relation between θ and E, where E is the energy of the scattered photon, can be found in standard texts on nuclear physics.* Scattered photons reaching the detector with energy in a small interval centered at E were assumed to yield a Gaussian pulse height distribution with 9.1 per cent full width at half maximum centered at the pulse height equivalent of E.

The radiation emerging from the end of the cylinder consists of a mixture of scattered and unscattered radiation. The pulse spectrum in the detector will depend on the ratio of scattered to unscattered radiation. The effect of the unscattered radiation in

* For example: SEGRE, E. Experimental Nuclear Physics. Part II. Volume I. John Wiley & Sons, Inc., New York, 1953, p. 319.

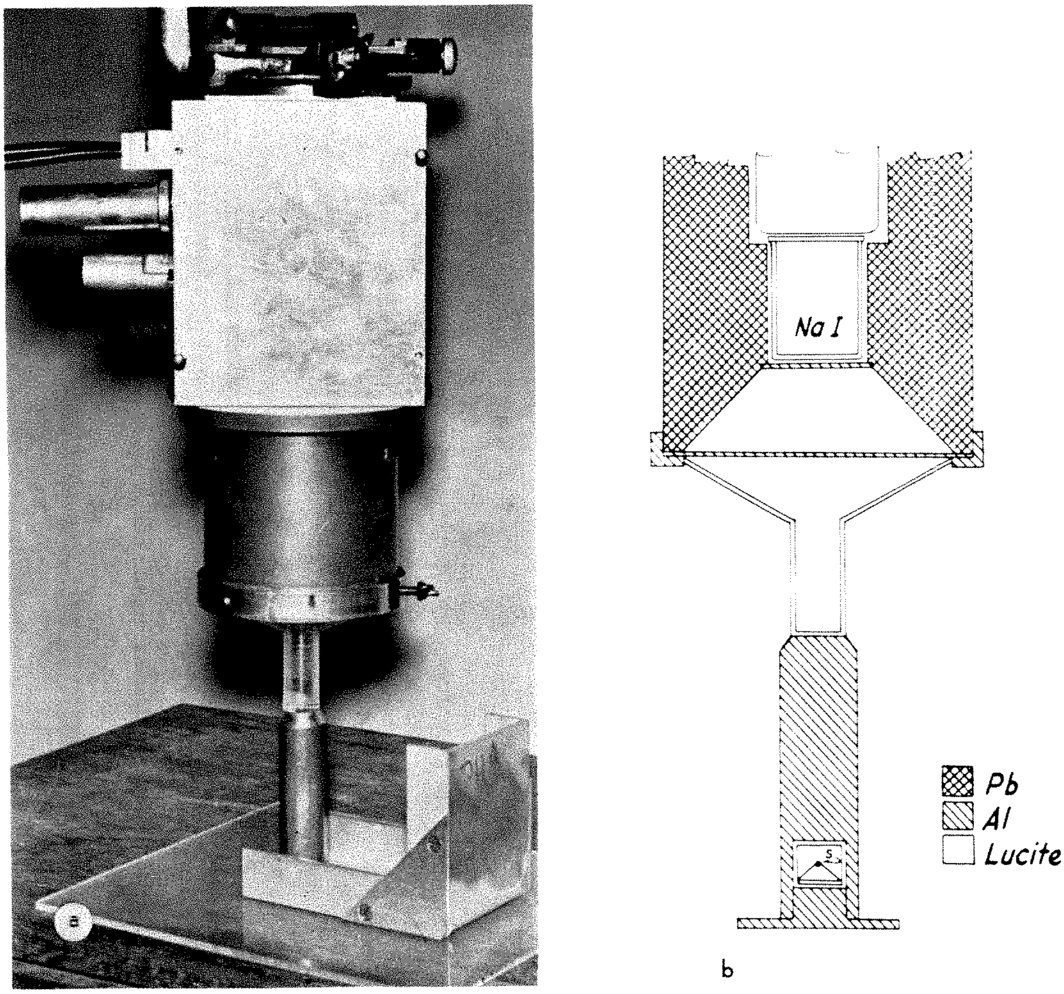

Fig. 5. (*a*) The physical arrangement of Cs^{137}-in-Al source in relation to our detector. (*b*) Diagram of *a*.

the detector can be represented by the dashed curve *a*, shown in Figures 7, 8, 9 and 10. Curve *a* is a pulse spectrum from a Cs^{137} point source taken with 9.1 per cent resolution (ratio of full width at half height to the abscissa at the maximum of the peak). Curve *a* is normalized so that the area under it above 42.5 volts represents 100 pulses.

The calculated effect of the scattered radiation in the detector is shown for a range of scattering masses by the dashed curves *b* to *h*, inclusive, of Figures 7, 8, 9 and 10. These curves show the expected number of pulses per volt pulse height interval due to scattered radiation per 100 total-energy pulses due to unscattered radiation. By the expression "total-energy pulse" is meant a pulse in the detector resulting from conversion of the total photon energy into light and therefore contributing to the peak of curve *a*. To obtain the predicted total pulse spectrum, the ordinates of any one of the curves *b*, *c*, *d*, etc., add directly to the corresponding ordinates of curve *a*.

The curves *b*, *c*, *d*, and *e* of Figure 7 display the calculated trend in the scatter spectrum as the cylinder length is varied keeping *R* constant at 1.25 inches. The values of *L* are respectively 1.5, 3.0, 6.0, and 10 inches. The curves *g*, *f*, *d*, and *h* of Figure 8 display the trend as radius and length are varied together, the ratio *R*/*L* being kept constant at 0.21. The values of

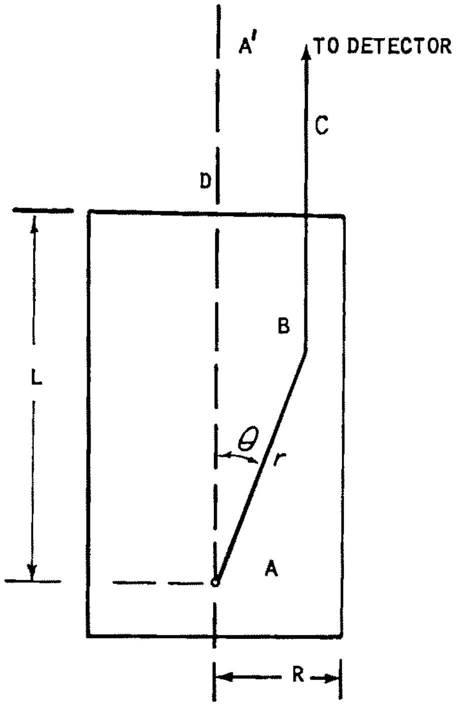

FIG. 6. Diagram of aluminum scattering cylinder with Cs^{137} point source at A, showing typical path by which a photon could reach the detector after being Compton scattered through an angle θ.

L are respectively 2.4, 3.5, 6.0, and 9.6 inches—the curve d being one of the family of curves in Figure 7. Figures 9 and 10 are comparisons between calculation and experiment. Figure 9 is a plot for the cylinder where $R=1.25$ inches and $L=6$ inches. The solid curve represents the calculated total pulse spectrum. It is the sum of a and d, which are repeated from previous figures. The circles are experimental points taken with a multichannel analyzer with approximately half volt channels. For comparison are shown (black crosses) the experimental points obtained from an I^{131} sample taken under the same conditions. The I^{131} sample was in the usual clinical form of a 30 ml. water solution of I^{131} salt, since this was the form the Cs^{137} sample was intended to simulate. Figure 10 is similar to Figure 9 except for dimensions of the scatterer. For Figure 10, $L=3.5$ inches and $R=0.75$ inches. The experimental points of Figures 9 and 10 were taken with 9.1 per cent resolution for the Cs^{137} point source. The statistical uncertainties in the experimental points vary from about 6 per cent for the lowest point to less that 3 per cent for the highest.

The calculations evidently furnish a fairly reliable estimate of the amount of scattering to be expected. As indicated by the data of Figures 9 and 10, the calculations underestimate the scattering, as might be expected from neglecting the possibility of more than one large angle scattering per photon. It is clearly not possible with a cylinder of homogeneous scattering material to achieve a concentration of scattered radiation in a small energy interval. This conclusion is especially important with respect to energy intervals close to 660 kev. It is therefore not possible to broaden the total energy peak in an arbitrary manner.

From Figures 7 and 8, it is clear that the

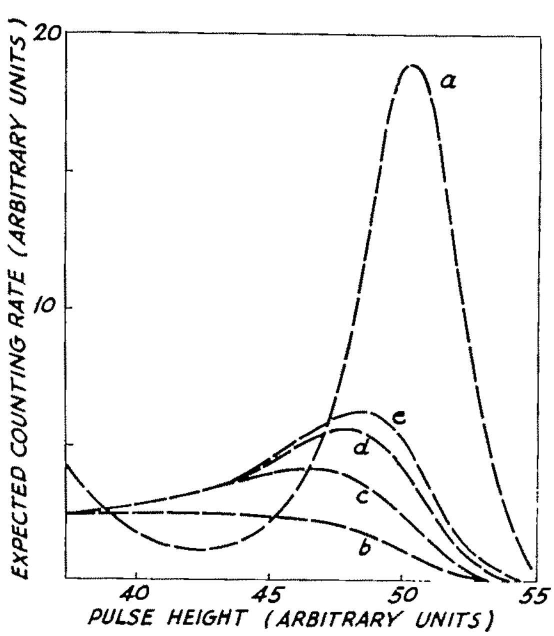

FIG. 7. Calculated spectra of scattered radiation from aluminum cylinders with 1.25 in. R and varying lengths: b, $L=1.5$ in.; c, $L=3.0$ in.; d, $L=6.0$ in.; e, $L=10$ in. The normalized Cs^{137} point source curve a shows the effect of unscattered radiation reaching the detector. The scattered radiation is calculated in all cases for the amount of unscattered radiation given by curve a.

intensity of the scattered spectrum increases with increasing mass of scatterer for proportions in which the length is several times the diameter. For a given diameter, the center of gravity of the scattered spectrum tends to higher energy (smaller scattering angle θ) as the length increases, up to a few diameters. However, as illustrated by a comparison of curves *d* and *e* in Figure 7, material far from the source in a very long scatterer contributes relatively little to the spectrum.

It is possible to approximate the I^{131} spectrum fairly well on the low energy side of the peak. This is quite satisfactory for our application, in which the lower and upper biases of the pulse height analyzer are well away from the peak base. The scatterer of Figure 10 somewhat overcompensates since the area under a curve through the I^{131} points would be somewhat greater than the area under one through the Cs^{137}-plus-scatterer points above a suitable lower bias

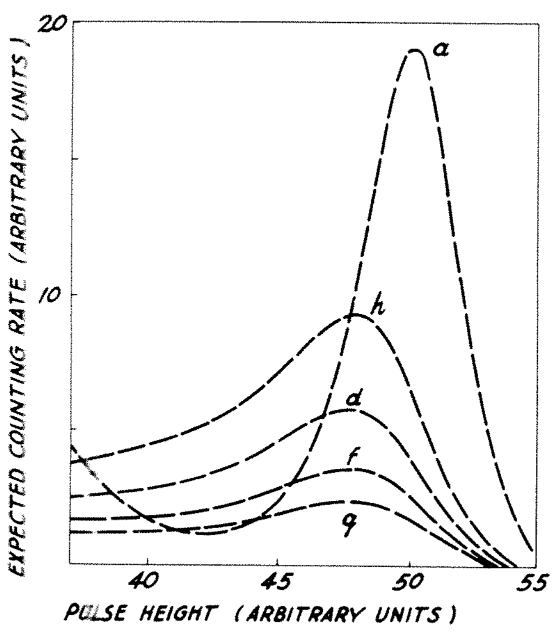

Fig. 8. Same as Figure 7 except that R and L are varied in constant proportion: g, $R=0.50$ in. and $L=2.4$ in.; f, $R=0.75$ in. and $L=3.5$ in.; d, $R=1.25$ in. and $L=6.0$ in.; h, $R=2.0$ in. and $L=9.6$ in. Normalization is to the amount of unscattered radiation reaching the detector shown by curve *a*.

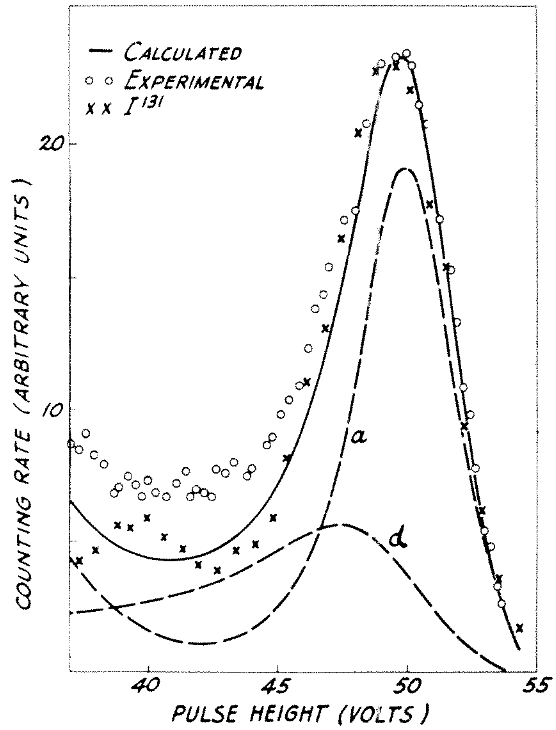

Fig. 9. Comparison of calculated and measured total spectra from a Cs^{137} source in a 1.25 in. $R \times 6$ in. L aluminum scatterer. The calculated solid curve is the sum of *a* and *d*. A measured spectrum from I^{131} in 30 ml. water is shown for comparison.

position such as 42.5 volts. The standard we use provides somewhat less than optimum scattering. Final choice of dimensions must depend on data like those of Figure 4, which show relative changes in counting rates of I^{131} and the Cs^{137}-in-Al for small gain and bias variations under otherwise standard operating conditions.

The fact that choice of operating conditions establishes the requirements placed on design of the source has been mentioned. The problem of tailoring the Cs^{137} spectrum to the I^{131} spectrum for clinical standardization can only be attacked after a choice of clinical operating conditions is made. The fact that we have chosen the aluminum dimensions to give a best correspondence between the spectra at 19 volts was governed by our previously made choice of the 19–26 volt interval in the I^{131} spectrum with the peak at 22.5 volts. This choice has some arbitrariness, but it appears to us to mini-

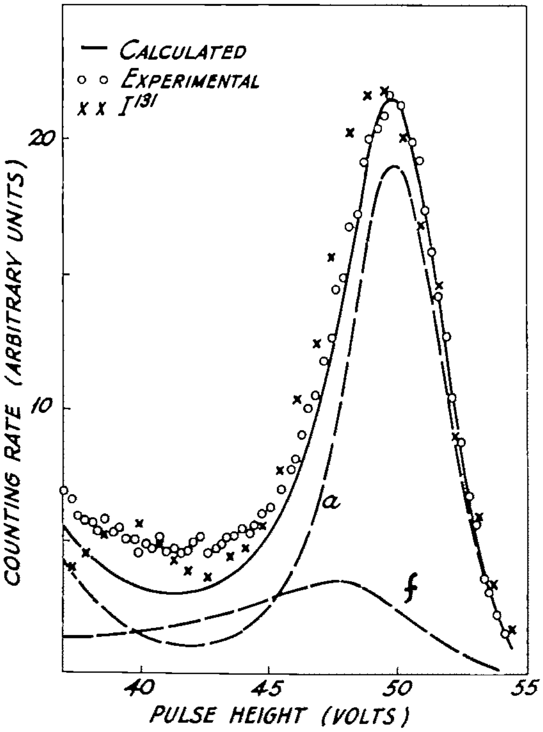

FIG. 10. Same as Figure 9 except that the scattering cylinder dimensions are: $R=0.75$ in. and $L=3.5$ in.

mize the effect on the I^{131} reading of gain and bias variations. Since the upper channel bias rejects relatively few pulses, there is no problem from overload of the anticoincidence circuits, and channel width need not be maintained to high accuracy. The choice of a lower bias at 19 volts minimizes dependence of the counting rate on the lower bias position, as is obvious from inspection of Figures 2 and 3, which show that the lowest point of the I^{131} spectrum occurs here. Possible deterioration of photomultiplier resolution with time makes it desirable to set the lower bias somewhat away from the peak. The peak broadening would thus be felt earlier at 19.5 than at 19.0 volts. The possibility of matching the I^{131} pulse spectrum in this region by introducing scattered radiation in the Cs^{137} standard spectrum strengthens the argument for the choice. It is probably needless to remark that inclusion of the total peak is desirable in order to obtain the best counting rates for the lowest dosages without sacrificing the advantages of pulse height analysis.

RESULTS

Over a period of two years, consistency of measurements within 2 per cent has been obtained on readings of the standard and on readings of I^{131} samples where activities have been accurately determined by established assay procedures. A single Cs^{137}-in-Al standard has been used throughout this period, obviating the expenditure of time in preparing short-lived standards and creating confidence in the long term stability of the measuring procedures. Photomultiplier changes were necessary on the average only once per instrument during this period. When the resistor ratio $r_2/(r_2+r_1)$ was readjusted to bring the I^{131} and Cs^{137}-in-Al peaks into coincidence after these replacements, recalibration with sufficient statistical accuracy showed that the counting rate from the Cs^{137}-in-Al had remained within 1 per cent of the value observed prior to replacement. Further observations after replacement have always confirmed constancy of this value. Thus the results justify the amount of effort expended in the initial calibration. Investigation of instrument performance when the standard value deviates from the accepted value consistently by 2 per cent has always indicated malfunction in the gain and bias circuits which was undetected by conventional methods.

A further advantage has been the ability to assess changes in millicurie value when dealing infrequently with large amounts of I^{131}. When the analyzer amplifier system is in good operative condition, amounts of I^{131} varying from 2 microcuries to 7 millicuries may be counted using lead absorbers. Minor electronic changes which cause a shift in millicurie value may occur, but are readily detectable by the use of the long-lived standard. Thus, shifts in millicurie value observed on any particular amount of I^{131} may be traced to either electronic malfunction or true error in dose preparation.

This paper has been written with the

conviction that simplification of calibration, maintenance and measurement techniques are an important and too often neglected aspect of the introduction of new equipment and methods into medical clinics and laboratories. We believe that some of the details of this procedure represent time-saving simplifications of current methods.

SUMMARY

Simple and accurate methods for calibrating and maintaining the accuracy of equipment using pulse height analysis for clinical I^{131} measurements have been worked out. Complicated procedures involving knowledge of electronics and nuclear physics were avoided.

The most important detail involved the use of a long-lived Cs^{137} standard which was made to simulate the characteristics of I^{131} by: (1) installation of a resistor set and switch in the linear amplifier such that superimposition of the cesium and iodine curve occurs; and (2) modification of the Cs^{137} pulse spectrum by limited use of Compton scattering in an aluminum shield.

Over a period greater than two years, consistency of measurements within 2 per cent has been obtained.

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THE SYNDROME OF EXOPHTHALMOS, HYPERTROPHIC OSTEOARTHROPATHY, AND PRETIBIAL MYXEDEMA

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THIS is a report of an adult Negro female who developed hypertrophic osteoarthropathy and pretibial myxedema following I^{131} induced remission of an exophthalmic goiter.

REPORT OF A CASE

The patient, a fifty-three year old Negro female, had noted the onset of easy fatigability, heat intolerance, and persistent night sweats about three years prior to her present admission to the hospital. She had also noted some weight loss at that time in spite of an increase in appetite. The thyroid was enlarged, smooth, and firm. There was bilateral exophthalmos. The palms of her hands were moist and there was a definite tremor. The blood cholesterol was 175 mg. per cent (normal 140–240 mg. per cent), protein bound iodine was 10.5 μg. per cent (normal 4–8 μg. per cent), and radioactive iodine uptake was 67 per cent (normal 17–37 per cent).

She was given 7 mc I^{131} and, over the next year, gained approximately 23 pounds and felt less nervous. The blood cholesterol rose to 282 mg. per cent and the protein bound iodine fell to 1.7 μg. per cent. The radioactive iodine uptake was recorded as 4 per cent. The clinical impression was hypothyroidism and she was placed on 1.5 gr. of thyroid extract per day. In spite of the thyroid therapy her hypothyroid state persisted

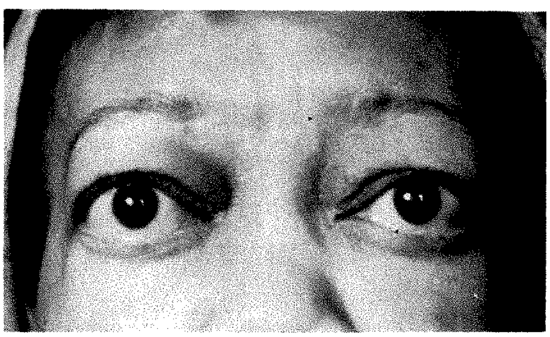

FIG. 1. Photograph showing the degree of exophthalmos present after thyroid therapy over a period of approximately two years.

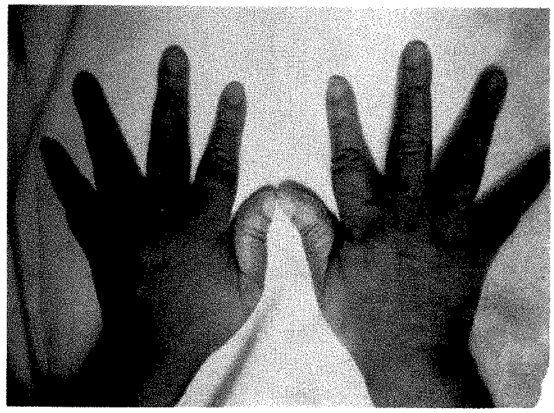

FIG. 2. Photograph showing swollen hands and fingers.

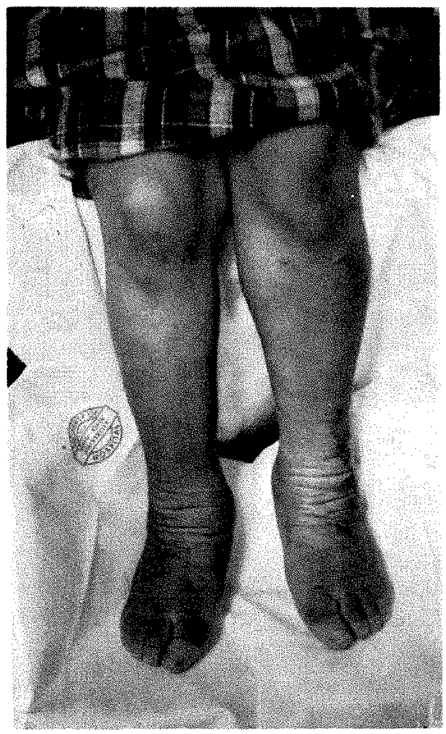

FIG. 3. Photograph showing thickened and wrinkled skin, particularly about the anterior aspect of the ankles.

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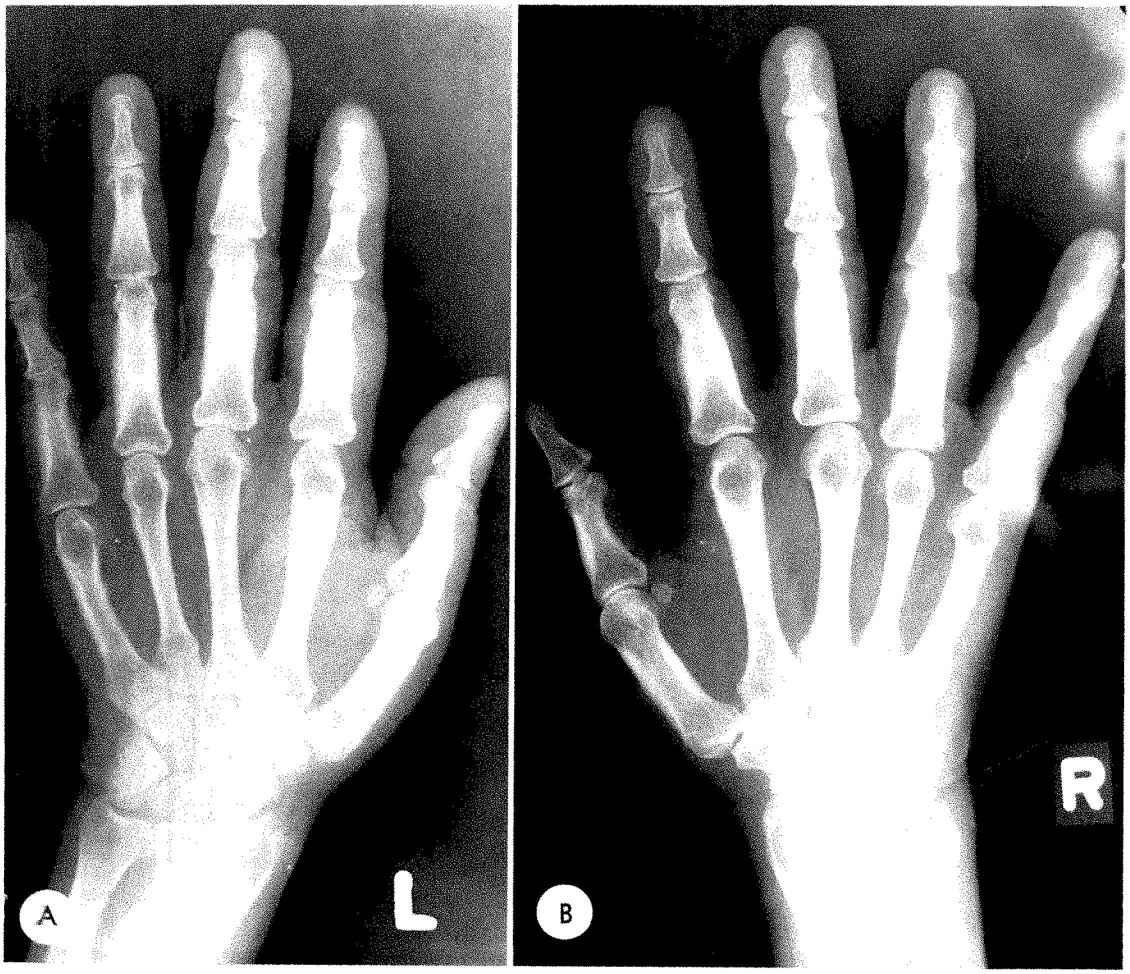

Fig. 4. (*A* and *B*) Roentgenograms of the hands showing diffuse, symmetric, periosteal new bone formation about the shafts of the proximal phalanges and both first metacarpals. Compare *A* with Figure 5.

over the next two years with the gradual development of progressive swelling of her hands, legs, and ankles.

With this history, the patient was admitted to the hospital where a skin biopsy from her left ankle was interpreted as showing changes compatible with myxedema. The basal metabolic rate was minus 12 per cent and the radioactive iodine uptake was 6 per cent. Exophthalmometric records had shown progressive increase in the degree of her exophthalmos. Figure 1 is a photograph taken on this admission. Other pertinent physical findings were swollen but nontender hands and fingers (Fig. 2). The skin of the legs, particularly about the anterior aspect of the ankles, was thickened and wrinkled (Fig. 3).

Roentgenograms of the hands (Fig. 4, *A* and *B*) showed diffuse, symmetric, periosteal new bone formation about the shafts of the proximal phalanges and both first metacarpals. We were fortunate in having an earlier roentgenogram of the patient's left hand (Fig. 5) which showed normal osseous structures four years earlier. In the feet (Fig. 6) the same, very symmetric, periosteal new bone development was seen in the first metatarsals bilaterally and, to a lesser extent, in the other metatarsals. The phalanges showed only minimal involvement. A chest roentgenogram showed no mediastinal or pulmonary pathology except for chronic fibrocalcific disease in the left upper lobe.

DISCUSSION

Hypertrophic osteoarthropathy was first described as an ossifying periostitis by

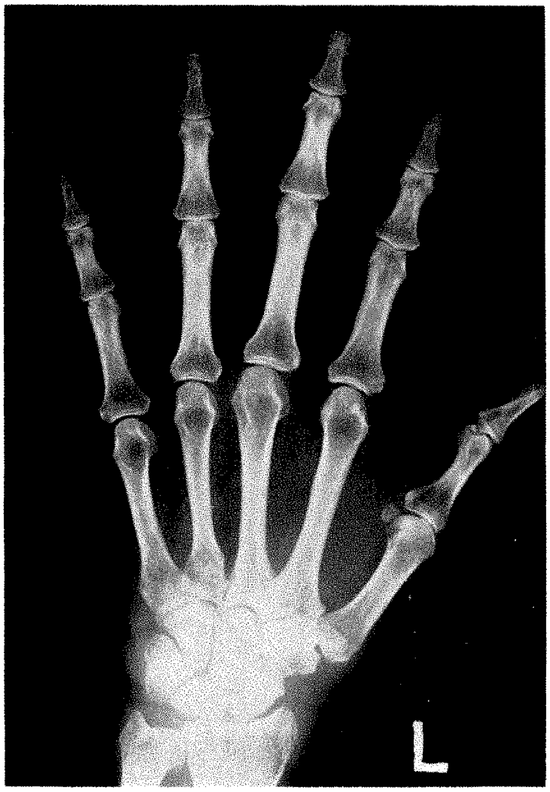

Fig. 5. Roentgenogram of the left hand, made four years before Figure 4*A*, showing normal osseous structures.

Bamberger in 1889. This condition is usually characterized by clubbing of the fingers and toes, an unusual nonpitting edema of the distal portions of the extremities, and subperiosteal proliferation of bone. Hitherto this condition has been described as being secondary to suppurative intrathoracic lesions, mediastinal new growths, tumors of the lung, abscess of the liver, pyelonephritis, cirrhosis of the liver with jaundice, certain obstructive lesions of the gastrointestinal tract, possibly syphilis, and perhaps congenital heart disease. In some cases the condition has been described as characterized by the absence of a discoverable primary disease and by the tendency for this syndrome to have a familial occurrence. Thus, hypertrophic osteoarthropathy is seen in association with a wide variety of primary diseases but it has only rarely been observed with diseases of the thyroid. There is no single hypothesis that adequately explains the syndrome.

The new bone is confined to portions of the skeleton which are covered by periosteum and is not seen in the joints, although involvement of the end of the bone may lead to disability in the joint itself. The change in the bone consists of a deposition of new bone between the cortex and the periosteum, particularly in the lower ends of the bones of the forearm and the lower leg and in the metacarpal and metatarsal bones. In extreme cases, similar changes have been described in the clavicles, ribs, pelvic bones, scapulae, malar bones, and even in the transverse processes of the vertebrae. Histologically, the cortical part of the bone shows little if any change. One extraordinary feature of the syndrome is the symmetry of the process, with the same portions of the same bones of the two hands involved to approximately the same degree.

Danforth and Humphrey[2] recently reported a case of a forty-six year old Negro male treated for hyperthyroidism with 12 mc of I^{131}. One year later he noted swelling of his legs with thickening and hardening of the skin in the pretibial region. A biopsy of this area of the skin was typical of pretibial myxedema. Roentgenograms showed minimal periosteal new bone formation involving several metacarpals and proximal phalanges bilaterally. Greene[5] described a seventy-four year old male who was treated eighteen years previously with potassium iodide for exophthalmic goiter. The goiter disappeared with the iodide therapy but about fifteen years later his eyes became prominent and he developed a remarkable degree of clubbing of the fingers. There was also some pretibial thickening of the skin regarded as possible pretibial myxedema. Roentgenograms of the hands revealed subperiosteal new bone formation along the shafts of the phalanges and metacarpals. Additional similar cases following subtotal thyroidectomy have been described by Thomas,[7] Diamond,[3] and Rynearson and Sacasa.[6]

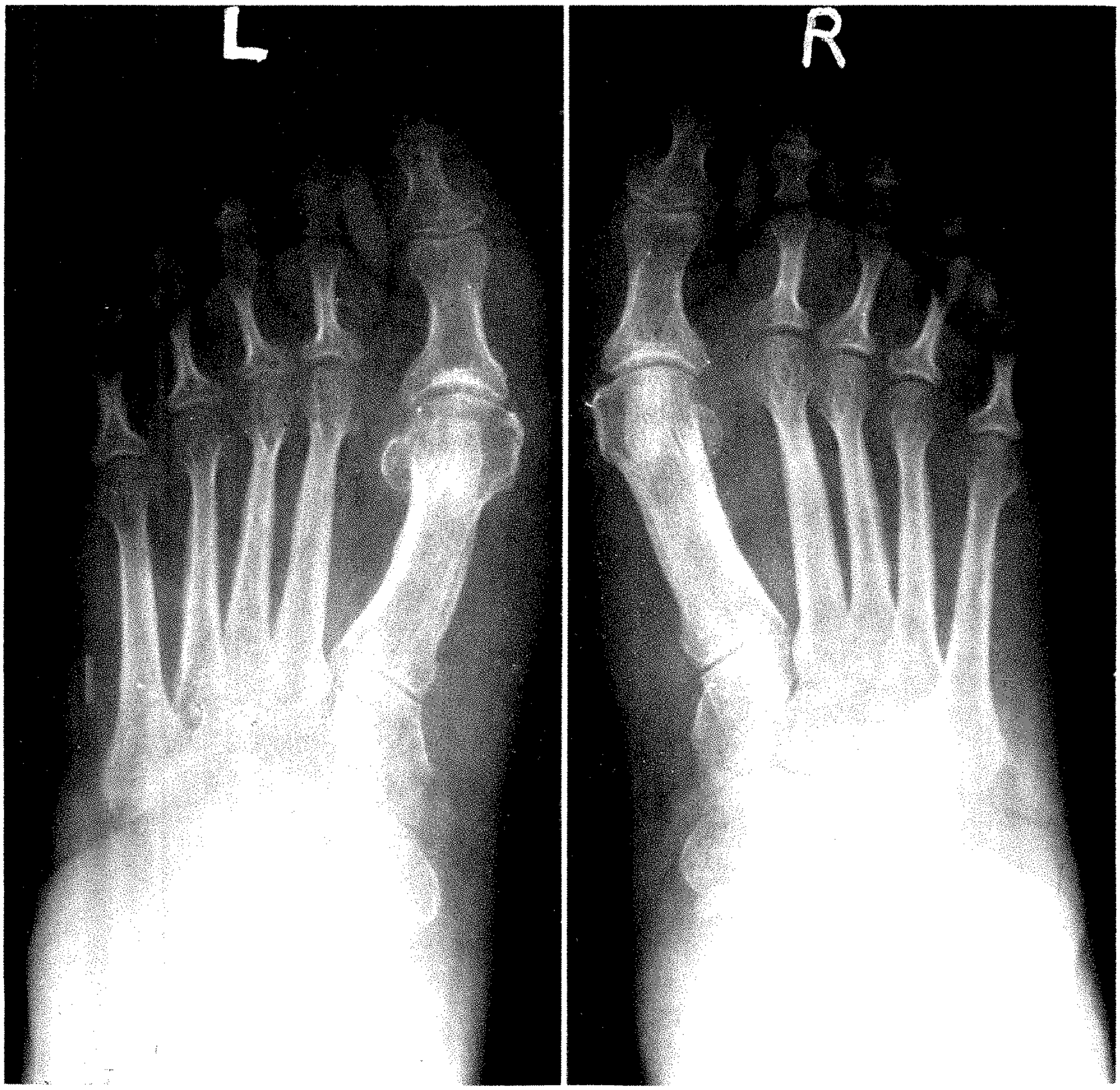

FIG. 6. Roentgenograms of the feet demonstrating symmetric, periosteal new bone development in the metatarsals, especially obvious in the first metatarsals.

Camp and Scanlan[1] presented 5 cases of hypertrophic osteoarthropathy without apparently known cause. One of these cases is similar to that presented in this article in that the patient developed myxedema and exophthalmos with massive enlargement of all the bones of the extremities due to subperiosteal proliferation in the diaphyseal portions.

Findlay and Oosthuizen[4] described a condition known as the syndrome of pachydermoperiostosis, in which thick furrowed skin is found particularly on the forehead, upper eyelids, and palms and is associated with hyperostosis. These authors describe this condition as a specific entity and attempt to differentiate it from thyroid osteoarthropathy.

SUMMARY

The occurrence of hypertrophic osteoarthropathy in association with exophthalmos and pretibial myxedema forms a rare syndrome of treated hyperthyroidism. These findings apparently have no rational explanation as regards thyroid function,

THE EXCRETION OF RADIOACTIVE IODIPAMIDE (CHOLOGRAFIN) BY NORMAL AND CIRRHOTIC MALES*

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SINCE the introduction of iodipamide (cholografin) as an intravenous cholangiographic agent,[2] it has been observed that in the presence of chronic hepatic disease the contrast medium is excreted through the kidneys rather than through the liver and biliary passages.[1,2,6] The introduction of cholografin labelled with I^{131} has made available an easily detectable form of the medium. Using this preparation, attempts have been made to measure quantitatively the excretion of radioactive cholografin in humans and animals with normal and abnormal liver function.[3,4,5,7] This study compares the excretion of radioactive cholografin by cirrhotics and patients with apparently normal hepatic function.

MATERIAL AND METHODS

Thirty-seven male patients at the Philadelphia Veterans Administration Hospital were studied. Twenty-two of these had normal hepatic function as measured by the usual screening tests. The remaining 15 were diagnosed as having cirrhosis of the liver by the appropriate clinical and laboratory criteria and/or by liver biopsy (Table II).

Cholografin labelled with I^{131} of very high specific activity (average about 1 mc/ml.) was obtained from a commercial supplier† and was used throughout the study. From each new purchase an assay for specific activity was done. Exactly 10 μc of the solution was diluted with sterile physiologic saline solution to a volume of 12 ml. Ten milliliters of this solution (containing about 8 μc of radiocholografin) were injected intravenously into patients who had been previously fasted for about eight hours.

The patients were studied by several means, including serial serum radioactivity determinations, 2 hour fractional and 24 hour fractional and 24 hour urinary radioactivity determinations, and by external counting over the liver and thyroid in some patients. The urine of several patients was also studied at 48 and 72 hours.

As a standard, 1 ml. of the original solution as diluted and prepared for injection was further diluted to 100 ml. in water, and a 2 ml. aliquot of this dilute solution was assayed for radioactivity by being placed in a crystal well counter and assayed for a sufficient length of time to give a ±3 per cent standard counting variation error (5 to 10 minutes), using a single channel gamma-ray scintillation spectrometer. The urine samples were assayed by similarly counting a 2 ml. sample of the urine specimen, and the percentage excretion was obtained by use of the following formula:

$$\% \text{ excretion} = \frac{\text{cpm (2 ml. urine)} \times \text{vol. of urine}}{\text{cpm (2 ml. of standard)} \times 10}$$

Serum radioactivity was obtained by assaying 2 ml. of serum in a similar manner. External counting over the liver and thyroid was done by the usual techniques used for the latter and, in the case of the liver, by centering the tube over a point halfway between the midclavicular and anterior

† Supplied by E. R. Squibb & Sons (Division of the Olin Mathieson Chemical Corporation).

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TABLE I

COMPARISON OF URINARY EXCRETION OF RADIOACTIVE CHOLOGRAFIN IN NORMAL INDIVIDUALS AND CIRRHOTICS

	24 Hour Urinary Excretion of Radioactive Cholografin (per cent of total)		
	<12%	12–14%	>14%
Cirrhotics	3 (20%)	2 (13%)	10 (67%)
Normals	16 (72%)	3 (14%)	3 (14%)

axillary lines, 5 cm. below the top of the liver as determined by percussion.

RESULTS

We were unable to demonstrate any significant difference between the normal subjects and the cirrhotics in the level of serum radioactivity, the rate of change of this level, or in the external counts over the liver, and these methods were therefore abandoned after the first few subjects were so studied. There was, however, a difference between the groups both in the rate of urinary excretion and the total 24 hour urinary excretion. These results are summarized in Tables I, II and III and in Figure 1. Three of the cirrhotics, or 20 per cent, had 24 hour excretions of radioactive cholografin of less than 12 per cent, while 16 of the normals, or 72 per cent, fell below this level. Two, or 13 per cent, of the cirrhotics and 3, or 14 per cent, of the normals fell into a 12 to 14 per cent range. Finally, 10, or 67 per cent, of the cirrhotics and 3, or 14 per cent, of the normals were above 14 per cent. The highest value in a normal patient was 18.9 per cent, while values for cirrhotics ranged up to 45 per cent in this study. There was detectable activity over the thyroid in all patients studied for such activity.

DISCUSSION

The accurate measurement of 2 hour fractional urine samples required the insertion of an indwelling bladder catheter with the attendant discomfort to the subject, danger of infection and added burden to the nursing personnel. We, therefore, felt that a single 24 hour collection would be preferable if the results corresponded. This proved to be the case (Fig. 1).

The presence of countable radiation over the thyroid gland indicates that in the

TABLE II

LABORATORY DATA AND CHOLOGRAFIN EXCRETION IN 15 PATIENTS WITH CIRRHOSIS OF THE LIVER

Patient	Age	BSP Retention* (per cent)	Alkaline Phosphatase (Shinawara units)	Bilirubin (mg./100 ml.)	Tissue Diagnosis	24 Hour Urinary Radioactive Cholografin (per cent of total)
S.R.	46	63	12.0	38.6	No	17.2
V.I.	43	26.5	14.8	4.7	Yes	19.5
E.R.	37	43	11.1	4.3	Yes	24.0
C.D.	36	37.5	11.7	30.6	No	15.3
J.M.	61	37.5	9.2		Yes	9.0
J.L.	45	23		2.9	No	14.4
P.L.	51	37.5	4.9	0.9	No	8.0
B.P.	39	30	19.9	2.2	No	15.9
C.T.	44	22	12	1.4	No	5.0
J.B.	56	26.5	7.1		No	45.0
J.S.	36	38.5	5.9	4.4	No	14.7
S.B.	44	31	16.5	1.0	Yes	19.3
S.R.	53	42	10.2	5.3	Yes	34.7
M.K.	62	33	7.7	2.7	No	13.0
B.H.	33	25.5	7.9	1.4	Yes	12.3

* Using 5 mg. per kg. of body weight and checking retention after 45 minutes.

Table III

LABORATORY AND CLINICAL DATA ON 6 OUT OF 22 PATIENTS WITH APPARENTLY NORMAL HEPATIC FUNCTION WHO HAD ELEVATED 24 HOUR RADIOACTIVE CHOLOGRAFIN EXCRETION

Patient	Age	24 Hour Urinary Radioactive Cholografin (per cent of total)	Laboratory and Clinical Data
C.L.	46	18.7	BSP, alkaline phosphatase normal; convalescent myocardial infarction
E.T.	59	13	BSP normal; rheumatic heart disease, congestive failure
T.K.	38	14	BSP, alkaline phosphatase, bilirubin normal; acute pancreatitis, alcoholism
E.A.	46	14.1	Alkaline phosphatase normal; coronary insufficiency
R.S.	44	18	BSP, alkaline phosphatase normal; erythema multiforme; steroid therapy
W.H.	37	13.1	Alkaline phosphatase normal; atopic dermatitis; steroid therapy

material as prepared there is a definite amount of free I^{131} available to the gland. No quantitative estimates of this were made.

Due to the high specific activity of the compound used, the dose of cholografin employed was less than that used for skin testing for sensitivity prior to gallbladder roentgenography. One would, therefore, not expect to see sensitivity reactions in the use of this amount of contrast material.

The results obtained confirm the fact that, in the presence of hepatic disease, radioactive cholografin is excreted through

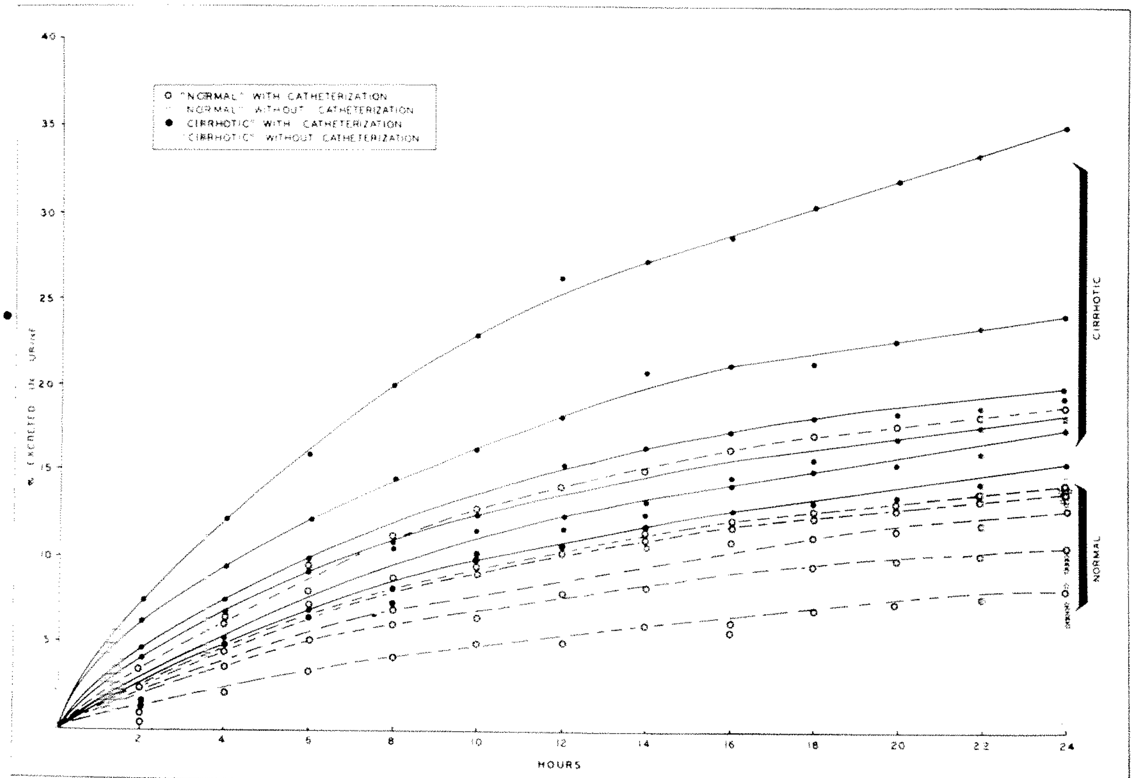

Fig. 1. Graph showing excretion of radioactive cholografin in normal and cirrhotic males.

the kidneys rather than through the liver and biliary passages.

CONCLUSIONS

Cholografin labelled with I^{131} injected intravenously into 37 normal and cirrhotic subjects gave urinary excretions differing significantly between both groups, both in total excretion and in rate of excretion. With few exceptions cirrhotics excreted a larger percentage of the contrast material in 24 hours and at a more rapid rate than normals. The total excretion and rate of excretion mirrored each other in all cases. Study of the urinary excretion of radioactive cholografin at the end of 48 and 72 hours yielded no information additional to that already obtained

There was detectable radioactivity over the thyroid gland in all patients so studied. Counting of blood samples and external counting over the liver failed to differentiate between the two groups.

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SCINTISCANNING OF DOG KIDNEYS USING DIODRAST I^{131}*

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METHODS for delineating renal parenchymal defects caused by neoplasm or cyst using intravenous pyelography or angiography reveal secondary distortion in either calyceal appearance or vascular distribution after the tumor has reached sufficient size. It would be highly desirable to define the presence of a small renal tumor before such secondary manifestations appear. Because scanning methods using I^{131} have proved of great value in the diagnosis of nonfunctioning thyroid lesions such as adenoma, carcinoma or colloid cyst, an effort has been made to apply to renal scanning the same principles used in thyroid scanning. This paper is a report of an initial study carried out in dogs wherein the goals were: (1) to delineate renal tissue by scanning after administration of I^{131} labeled iodopyracet (diodrast), (2) to determine the body retention of this radioactive material and to calculate therefrom the radiation dosage to the whole body and blood, and (3) to determine if significant changes in blood count or body tissues would occur following the administration of radioactive material.

METHOD AND MATERIAL

Scanning Method. Sterile diodrast I^{131}† having a specific activity of approximately 10 mg. per 1 mc (range 1.5 to 16 mg.) was injected rapidly and undiluted into the tubing through which an infusion of 5 per cent dextrose in water was running. A tuberculin type syringe was used to measure and administer the material. The infusion was maintained at approximately 20 to 30 drops per minute throughout the study to permit rapid repeat intravenous injections.

In two preliminary studies, an injection of 1.4 gm. (4 cc. of 35 per cent solution) of stable diodrast was given prior to injection of diodrast I^{131} to try to retard excretion of I^{131} labeled dye and thus to maintain longer and better renal I^{131} concentration for scanning. Scans following this technique were unsatisfactory because concentration of I^{131} sufficient for scanning was not attained in the renal area at any time in a two hour period following injection of stable diodrast.

Ten mongrel dogs were given potassium iodide in their drinking water 2 days and 1 day prior to the study. Anesthesia with veterinary nembutal was maintained throughout the study period to assure accuracy and constancy of positioning. Scanning in the prone position was performed with a 1 inch by 1 inch sodium iodide (Th) scintillation crystal with collimation as described by Allen and Risser[1] using a motor driven constant speed scanner with print-out recording of I^{131} 364 kev. gamma ray defined by a research grade pulse height analyzer and linear amplifier.

In early studies the kidney was traversed by scans 5 mm. apart, and recording was made by a 2 mm. wide printing stylus. In later studies a 5 mm. printing stylus was used with the same 5 mm. scan spacing factor. Duration of scan of each kidney varied from 4 to 12 minutes and of the complete study from 10 to 21 minutes, depending on the speed setting of the motor drive. With settings of 0.45 cm./sec. scan speed, good definition was obtained in the scan. The scan of a single kidney was begun within one minute of injection of 100 to 200

† Obtained from Abbott Laboratories, Oak Ridge, Tennessee.

* From the Radioisotope, Radiology and Laboratory Services of the Veterans Administration Hospital, and the Department of Physics, The Rice Institute, Houston, Texas.

μc diodrast I^{131}. A second injection was made at the finish of scan of this kidney and immediately prior to the beginning of scan of the opposite kidney. Occasionally a third injection was required to maintain I^{131} concentration in the renal area. This technique was found more satisfactory than an earlier procedure of injecting a single large dose. In these early scanning trials with a single large dose, concentration of I^{131} had decreased to such degree that poor definition of renal outline was obtained in the areas scanned at 10 to 20 minutes after injection.

It is important, as in scanning other organs, that careful attention be paid in advance to peak location of the 364 kev. I^{131} gamma ray in the pulse height analyzer channel, and to speed, spacing and limits of area to be covered by the scan. Settings must be made in advance of actual performance of the scan, since the time of satisfactory recording is limited by rapid excretion[4] of the I^{131} labeled dye. Also, we found it useful to give a preliminary 20 to 25 μc dose for purposes of gross kidney location and of finding spacing and limit settings on the scanning controls. The total dosage, including the preliminary dose for completed satisfactory scans, ranged from 136 to 464 μc.

Assay Procedures. Eight adult mongrel dogs with preparation of potassium iodide in drinking water for 2 days prior to test and additional subcutaneous injection on the day prior to test received 340 to 400 μc diodrast I^{131} intravenously (using a foreleg vein). Radioassay and survey of body retention was performed in the following manner:

(1) Five cc. of blood was withdrawn from an external jugular vein at 30 minutes, 2 hours, 4 hours, 6 hours, 1 day, 2 days, 3 days, 5 or 6 days after injection. Radioactivity counting was done in a calibrated Texas well Geiger-Müller counter. Calculation of the radioactivity remaining in the total blood volume (estimated at 65 cc./kg. body weight) was made and the per cent of injected dose retained at each time was plotted on linear graph paper.

(2) Urine and feces were collected and assayed by aliquot removal; the total radioactivity excreted was calculated as the per cent of dose injected. These collections were continued for one week after injection.

In addition, 4 dogs with similar preparation received 400 μc diodrast I^{131} subcutaneously, and similar blood, urine and fecal studies were performed.

Blood and Tissue Studies. Four animals received 400 μc intravenously and serial studies of hematocrit, white blood cells and platelets were performed[5] up to 7 to 25 days following injection. All animals used for scanning studies were sacrificed at from 4 to 8 weeks following the study and tissues were examined grossly. Sections of thyroid, heart, lung, liver, spleen, pancreas, kidneys, urinary bladder and bone marrow were fixed with 10 per cent neutral formalin and examined microscopically after suitable fixation and staining with hematoxylin and eosin.

RESULTS

Scanning. Figure 1 is a scan of one of the animals. For this scan two doses of diodrast I^{131} (without preliminary stable diodrast injection) were given rapidly, the size of each dose being 105 μc. As soon as the scan of the left side was completed or nearing completion, the second dose was administered. A gross outline of renal parenchyma can be seen in the completed scan (Fig. 1). The time required for dose injection and scanning was 17 minutes. Similar results were obtained with this multiple dose split-scanning technique in 5 additional dogs. High vascular radioactivity was also seen in these scans, and the lower portion of liver and gallbladder was partially outlined when the scan was continued over the right upper flank.

Assay. Table 1 shows the per cent of injected I^{131} retained in the estimated total blood volume (based on body weight) in the dogs injected intravenously or subcutaneously with 139 to 400 μc diodrast

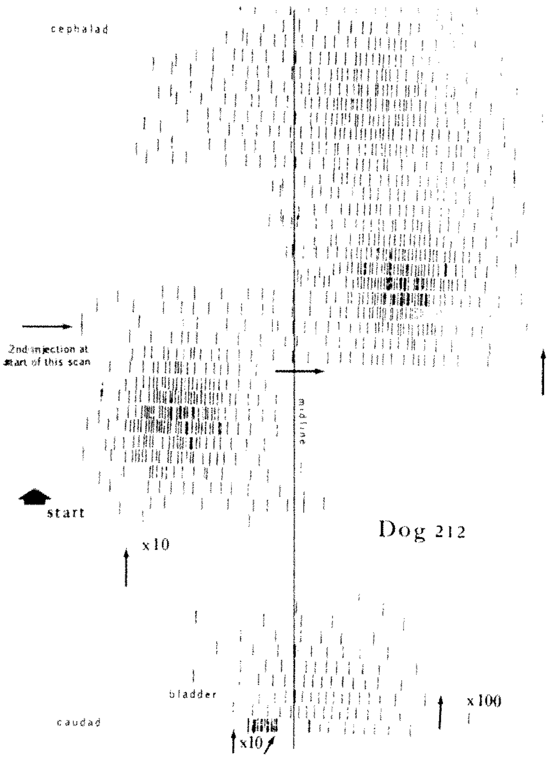

Fig. 1. Scan of renal areas performed as described in the text using two intravenous doses of diodrast I^{131} of 105 μc each. Both renal areas as well as liver and gallbladder areas are outlined by this technique. High background due to vascular content of radioactivity is apparent. A scaling factor of 10, as indicated, was used in the renal and hepatic areas; a factor of 100, as indicated, was used in the region of the bladder, where scanning was finally terminated.

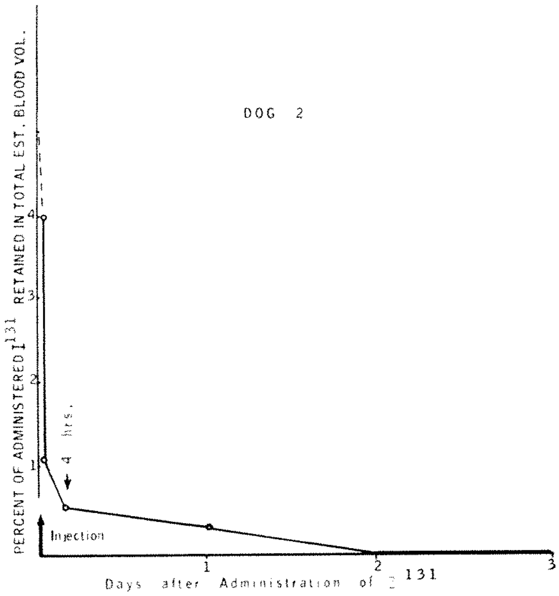

Fig. 2. Per cent retention of radioactivity in total estimated blood volume is shown in relation to time following intravenous injection of 340 μc I^{131} labeled diodrast.

I^{131}. As anticipated on the basis of previous data,[4] a rapid decrease in blood radioactivity was seen in those injected intravenously. In animals injected subcutaneously the radioactivity at 30 minutes was appreciable and fell rapidly thereafter, although minute amounts were still detectable as long as 96 hours after injection. The per cent of dose excreted in urine and feces in these animals in the week following injection ranged from 81 to 103 per cent, the major portion being excreted in the first 24 hours following injection. By linear graphing (Fig. 2) of the results of blood radioactivity assay, and measurement of the area under the curve throughout the first 24 hours, a calculation of rad dosage was made according to the method outlined by Quimby.[3] In the case of dog No. 9 (which retained the greatest amount in the series) 178 mrad/mc was delivered to the whole body. Dog No. 5 retained the smallest amount throughout the first 24 hours and was calculated to have received 25 mrad/mc whole body radiation exposure. Bone marrow and blood dosage is estimated to be two-thirds of the body value.[3]

Blood and Tissue Studies. Blood cell counts showed no significant change in animals studied for 7 to 25 days after injection. Microscopic examination of the various organs revealed no pathologic alterations in animals sacrificed up to 40 days.

DISCUSSION

On the basis of data from these studies, it appears feasible to attempt renal scanning in humans. This conclusion is based on the following considerations:

(1) If a large enough dose of diodrast I^{131} is administered, renal concentration of the I^{131} labeled dye remains sufficiently high for the period required to scan the renal area. Repeat doses may be utilized to

Table I

PER CENT OF INJECTED DOSE RETAINED IN TOTAL BLOOD VOLUME (ESTIMATED) FOLLOWING ADMINISTRATION OF DIODRAST I^{131} INTRAVENOUSLY OR SUBCUTANEOUSLY

Time after Injection (hr.)	Dog No.											
	1	2	3	4	5	6	7	8	9	10	11	12
	Route											
	I.V.	I.V.	I.V.	I.V.	I.V.	I.V.	I.V.	I.V.	S.C.	S.C.	S.C.	S.C.
	Dose (μc)											
	139	340	340	340	400	400	400	400	400	400	400	400
½	3.80	3.98	1.70	2.00	—	4.10	4.20	5.70	3.60	1.80	1.10	2.90
1	0.81	1.20	0.50	0.30	1.50	—	—	—	—	—	—	—
2	—	—	—	—	0.30	0.99	0.85	0.88	—	—	—	—
4	0.42	0.56	0.24	0.24	0.23	0.37	0.38	0.29	0.65	0.36	0.27	0.50
6	—	—	—	—	0.18	0.27	0.26	0.22	0.30	0.44	0.21	0.34
8	—	—	—	—	—	—	—	—	0.39	0.31	0.23	0.17
24	0.15	0.30	0.20	0.10	0.10	0.18	0.32	0.19	0.23	0.21	0.07	0.18
48	Bgnd	Bgnd	Bgnd	Bgnd	0.05	0.13	0.17	0.10	0.40	0.26	0.24	0.13
72	Bgnd	Bgnd	Bgnd	Bgnd	0.03	0.09	Bgnd	0.08	—	—	—	—
96	—	—	—	—	—	—	—	—	0.15	0.16	0.08	0.11
120	Bgnd	Bgnd	Bgnd	Bgnd	—	—	—	—	0.07	Bgnd	Bgnd	Bgnd
144					Bgnd	Bgnd	Bgnd	Bgnd	Bgnd	Bgnd	Bgnd	Bgnd

I.V. = intravenous.
S.C. = subcutaneous.
Bgnd = background.

maintain this concentration. Difficulties due to protein binding (occurring with a low stable diodrast content), as described by Block *et al.*,[2] do not occur with this high dosage, since the specific activity of available material is about 10 mg./mc. Total doses of the order of 2 to 2.5 mc probably will be required for a satisfactory scan in humans and, in this amount, the effect of protein binding will not be observable.

(2) When 2 to 2.5 mc I^{131} as diodrast is used, safety with regard to radiation damage to whole body and blood (including bone marrow) can be assumed, since total body exposure in the first 24 hours of 178 mrad/mc occurred in the dog with the maximal retention and usual values were in the range of 110 mrad/mc. Radiation dosage from intravenous pyelography or angiography may contribute as much or more radiation exposure[6] in the course of screening renal function or diagnosis of vascular or collecting abnormalities of the kidneys. In the case of intravenous pyelography with four anterior position exposures, up to 480 mr is calculated as the midplane tissue dose and 160 mr as the mean marrow dose. Renal scanning in humans with 2 to 2.5 mc should cause no more than 150 mrad exposure to marrow.

It should be possible, therefore, to scan individuals suspected of renal tumors in whom changes in intravenous pyelography appearances have not yet occurred. Thus, diagnostic information may be offered before secondary distortion and probable invasion of the collecting system or major vessels have developed. Furthermore, the method represents no technical hazard to the individual such as those occasionally encountered with angiography. No iodide sensitivity reactions are anticipated following intravenous injection, since amounts of stable diodrast injected are of the order

of 20 to 25 μg. in contrast to routine intravenous pyelography using 10 gm. diodrast, 15 gm. sodium diatrizoate (hypaque), or 15 gm. methylglucamine diatrizoate (renografin), all of which have iodine contents ranging from 59.9 per cent to 62.5 per cent. The preparation of the patient will require, however, prior thyroid blocking with Lugol's solution or tapazole to prevent the thyroid concentration of iodide I^{131} released from the labeled dye.

CONCLUSIONS

Scintiscanning of the kidneys of normal dogs was performed by use of 135 to 465 μc diodrast I^{131} administered intravenously in divided doses during the scanning procedure.

Radioassay procedures based on blood retention of radioactivity revealed a total body radiation exposure during the first 24 hours of 178 mrad/mc in the dog with the greatest blood retention. Excretion studies revealed nearly complete elimination of the administered radioactivity within 3 days, the major portion occurring in the first 24 hours.

No adverse effects on peripheral blood count or on tissues examined after autopsy could be found in animals given 400 μc diodrast I^{131} intravenously or subcutaneously.

The method appears to be feasible for human application where doses of the order of 2 to 2.5 mc are anticipated and where thyroid blockage of I^{131} uptake will be necessary.

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STAINING WITH I^{131} LABELED 4-IODOALIZARIN 3-SULFONIC ACID *IN VIVO*, A TRACER FOR GROWTH AREAS IN BONE*

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ALIZARIN is a well known[1-4] vital staining agent for new bone formation, especially in mammals. The staining of malignant new bone formation *in vivo* in humans was described for the first time by Schorr *et al.*[7] This study gave the stimulus for further experimental investigations in order to prepare a radioactive iodoalizarinate substance for eventual diagnostic and therapeutic effects in malignant bone conditions. The use of iodine derivatives of alizarin was suggested as a contrast medium for diagnostic roentgenography and as a radioactive tracer and a therapeutic agent. The purpose of this study is to evaluate the application of I^{131} labeled alizarin as a tracer and to determine the distribution of iodoalizarin in various organs and tissues.

METHOD OF STUDY

I^{131} labeled 4-iodoalizarin 3-sulfonic acid has been synthesized according to the method developed by Frankel and Moses.[5] A 0.05–1.0 per cent solution at various specific activities (μc per cc.) was injected intraperitoneally or intravenously into young white rats. (For practical purposes no difference was found between intraperitoneal and intravenous routes.) The rats were sacrificed at predetermined intervals and the specific activities in various organs were measured. The radioassay was performed on fresh tissues counted in a well type sodium iodide crystal scintillation counter.

Duplicate samples of the tissues examined were weighed and subsequently counted at a counting efficiency of 28 per cent. The organs which were investigated in this study included liver, spleen, thyroid and kidneys as well as samples of blood, brain, lungs and muscle. Of the bony tissues, the following were examined: the shafts and ends of femur and tibia, the skull, incisors and vertebrae. The determination of the specific activity (in μc per gm. of whole tissue) enabled us to follow the distribution of iodoalizarin in the organism. The results are presented below, either as specific activities (μc per gm. tissue), or as relative activity to blood (*i.e.*, the ratio of the specific activity in the respective tissue to the specific activity in the blood).

RESULTS

The relative distribution of 4-iodoalizarin 3-sulfonic acid (IASA) in various tissues is presented in Table I. The data of this table are compiled from distribution determinations done on 32 young rats (50–80 gm.).

From the data given in Table I it may be concluded that: (a) there exists a constant increase in time of the relative concentration of IASA in bone; only after one hundred hours following injection does the specific activity in bone exceed that in blood; (b) there is a constant increase in activity of the thyroid with time, which indicates that IASA is metabolized and deiodinated—and the iodide ions produced are trapped by the thyroid gland; and (c) there is an increase in time of the relative activity of practically all other tissues; this increase

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Table I

THE RELATIVE DISTRIBUTION OF 4-IODOALIZARIN 3-SULFONIC ACID IN CERTAIN TISSUES OF RATS*

Site	Time after Injection								
	¼ hr.	½ hr.	2 hr.	4 hr.	10 hr.	24 hr.	48 hr.	72 hr.	168 hr.
Blood	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Thyroid	0.32	0.46	0.54	0.93	1.37	3.65	10.7	22.3	130.00
Liver	1.15	0.83	0.94	0.76	0.68	0.82	1.43	1.7	
Spleen	0.89	1.17	1.03	0.73	0.64	0.84	1.63	2.1	
Lung	0.51	0.54	0.69	0.64	0.45	0.58	0.71	1.2	
Kidney	1.46	0.97	1.03	0.68	1.48	0.78	2.35	3.1	
Brain	0.013	0.018	0.022	0.025	0.038	0.045	0.13	0.18	
Muscle	0.14	0.14	0.16	0.18	0.22	0.31	0.30	0.29	0.86
Bone End	0.31	0.31	0.31	0.34	0.45	0.57	0.68	0.85	1.45

$$* \text{ Relative activity} = \frac{\text{Specific activity in tissue}}{\text{Specific activity in blood}}.$$

indicates some retention of IASA in various organs.

The deiodination of IASA made necessary a comparison between the relative accumulation in bone and the relative concentration of iodide in the same organ. The relative accumulation of iodide in bone has been determined at the following doses of injected iodide: 500 μg., 25 μg., and carrier free I^{131}. The results are presented in Table II.

Table II

THE RELATIVE DISTRIBUTION OF IODIDE IN BONES OF RATS*

Time after Injection (hr.)	Iodide Dose		
	500 μg.	25 μg.	Tracer I^{131}
4	0.56	0.56	0.49
8	0.54	—	0.50
24	0.45	—	0.44

$$* \text{ Relative distribution in bone} = \frac{\text{Specific activity in bone}}{\text{Specific activity in blood}}.$$

The relative distribution of IASA in certain bones is demonstrated in Table III. In this table the specific activities are given for the growing femur edges.

From Table III it may be seen that the accumulation of IASA in growing bone surpasses that in other bone areas. The fact that callus formation accumulates 7 times more IASA than the bone shafts in the same animal is worth noting.

The effect of IASA concentration on the distribution of IASA in various organs has

Table III

THE RELATIVE DISTRIBUTION OF 4-IODOALIZARIN 3-SULFONIC ACID IN BONES OF RATS

Site	Time after Injection							
	¼ hr.	½ hr.	2 hr.	4 hr.	10 hr.	24 hr.	48 hr.	72 hr.
Incisor	0.65	1.0	0.7	0.7	0.7	—	0.7	0.23
Skull	1.25	0.9	1.7	1.0	0.8	0.9	0.9	1.2
Vertebra	1.0	1.6	0.7	0.7	0.5	0.9	0.8	0.3
Shaft	1.3	0.9	1.1	1.1	0.8	0.73	0.52	0.33
Bone End	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Callus Formation	—	—	—	—	—	1.24	1.32	2.3

TABLE IV

THE EFFECT OF IASA CONCENTRATION ON ITS RELATIVE DISTRIBUTION*

	0.5 mg. IASA	5 mg. IASA	10 mg. IASA	0.25 mg. IASA + 2.5 mg. ASA
Blood	1.00	1.00	1.00	1.00
Spleen	0.33	2.75	1.90	1.60
Liver	0.80	0.45	0.74	0.45
Muscle	0.14	0.15	0.26	0.15
Brain	0.032	0.035	0.087	0.020
Bone End	0.31	0.55	0.53	0.49

* Relative concentration = $\frac{\text{tissue}}{\text{blood}}$ at eight hours after injection.

been investigated. Doses of 0.5, 5 and 10 mg. IASA have been administered and compared with a dose of 0.25 mg. plus 2.5 mg. of iodine free alizarin sulfonic acid (ASA). The results of this comparative study are given in Table IV.

From Table IV it may be concluded that the relative concentration of IASA in all organs, including bone, rises when we increase the dose of 0.5 mg. per rat tenfold. There is no further increase in the relative concentrations in bone when the dose is doubled from 5 to 10 mg. We may point out that there exists an increase in the relative concentration of IASA in bone in the presence of alizarin sulfonic acid. The relatively large accumulation of IASA in the spleen at high IASA and ASA doses should be noted.

The rate of excretion of IASA has been followed by calculating the biologic half life of the activity in various organs. The biologic half life was obtained by plotting the specific activity in a particular organ on a semilogarithmic plot versus time. The slope of the plot equals $0.693_{1/2}$. In Table V the biologic half life of IASA is compared to that obtained for iodine 131 by Perlman *et al.*[6]

From Table V it is evident that the rate of excretion of IASA is determined by more than a single factor since the biologic half life changes with time. We may note that the excretion of IASA from bone is much slower than from other organs. This behavior may be compared with that of iodine in the thyroid gland. Another analogy with iodine metabolism is the fact that the rate of excretion increases with the dose of IASA, though the effect is not as spectacular as in the case of iodine.

DISCUSSION

The data demonstrate that 4-iodoalizarin 3-sulfonic acid, like alizarin sulfonic acid, accumulates in bone, especially in areas of new bone formation. The relative highest accumulation of the dye occurs in bone callus (Table III). Nevertheless the accumulation of the iodinated dye in bone is not markedly higher than the level in blood. It should be noted, however, that the data in Table I are given in units of relative specific activity per unit weight. If we calculate the relative specific activity per unit volume, we would find that bone tissue activity is three times greater than is shown by the data given in Table I, due to the higher

TABLE V

THE BIOLOGIC HALF LIFE OF IASA AND I^{131} IN RATS

	0.5 mg. IASA		5 mg. IASA	0.5 mg. I^{131}	Tracer I^{131}	
	Up to 48 hr.	48–170 hr.	Up to 48 hr.	Up to 48 hr.	Up to 48 hr.	48–200 hr.
Blood	13	32	10	5.2	67	215
Muscle	14	28	11.5	—	—	—
Thyroid	—	—	—	21	60	200
Bone	16	132	13	—	—	—

density of bone. After a relatively long period (for instance, one hundred and seventy hours for rats) we find a fivefold local activity in the growing part of bone as compared to blood, and twice as much in callus areas. If we compare the behavior of the dye with that of injected iodide (Table II) it is found that, whereas the iodide or its organic bound forms accumulate in bone to some extent (never above blood level), its relative specific activity does not increase with time. This means that there is little retention of inorganic or protein bound iodine in bone. There exists little effect of the iodide concentration in blood on the relative concentration of iodide in bone, in contrast to other tissues like thyroid where one finds limited capacity for iodide.[6] In the case of IASA, we do find a positive effect of the concentration of the dye in blood on the relative activity in bone (Table IV). When the level in blood is increased there is an increase in the relative concentration in bone, which is contrary to the case of iodide in the thyroid gland.

Probably there is a limited rate of clearance of the dye through the kidney or the feces. The excretion through the kidney and intestines is hardly dependent on the blood concentration of the dye, thus enabling the bone tissue to accumulate a higher concentration of the dye in a given time, before the level in blood falls below that in bone. An interesting fact in this respect is that alizarin sulfonic acid helps iodoalizarin sulfonic acid to accumulate in bone, most probably by slowing down its rate of excretion. The rate of excretion of the dye is slower than that of iodide at the same range of concentration, though it is faster than that of iodide at tracer level. There is evidence (Table I) that IASA undergoes metabolization and is deiodinated at a relatively slow rate (approximate biologic half life of seventy hours). Consequently, after one hundred and seventy hours there is no dye left in the organism except that which had accumulated in bone; all the remaining activity in the body at this time is due to iodide and to protein bound iodine formed from the metabolized dye.

From the rates of excretion and metabolization of the dye, it may be calculated that, at the time when the specific activity in bone rises significantly above the activity of the blood, only 1 part in 300 of the injected dye is retained in the organism. This is mainly concentrated in the growing parts of the bone. Measuring a certain growing area of bone, or a malignant bone tissue, we may find only a small percentage of the amount of the retained dye. The amount of dye we may expect under these circumstances in a particular volume of bone may be, even under favorable conditions, below 1 part in 10,000 of the injected dose. Considering the application of the labeled dye as a tracer for growth areas in bone, this would mean a quite impractical initial dose of radioactive dye, even if we were to block the thyroid gland in order to avoid accumulation of iodide by the gland. The same reasoning would apply if 4-iodoalizarin were used as a contrast medium in roentgenography. In order to accumulate only 50 mg. of the dye in a certain volume it would be necessary for the patient to ingest 0.5 kg. of IASA.

We may conclude, therefore, that, although I^{131} alizarin sulfonic acid accumulates especially in areas of physiologic and pathologic new bone tissue formation, its efficiency of concentration, its rate of excretion, and the fact that it is metabolized make its application as a tracer impractical for clinical use. It is suggested that other chelating agents may have a higher affinity for bone, a lower rate of excretion and a higher stability, thus enabling them to be used as tracers or as contrast media for the study of bone.

SUMMARY

1. The distribution of 4-iodoalizarin 3-sulfonic acid in various organs has been determined, using I^{131} labeled dye. The organs examined included liver, spleen, thyroid, kidneys, blood, brain, lungs and muscle, with special reference to bone tissues.

2. It has been found that the labeled dye accumulates in bone, and especially in growing bone formations. The specific activity in bone exceeds that in blood only after most of the dye has been excreted. A comparative examination has been performed determining the accumulation in bone formation of I^{131} injected as an inorganic iodide.

3. It has been found that iodoalizarin undergoes metabolization and is deiodinated. The rate of excretion of iodoalizarin has been determined and compared to the rate of excretion of iodine injected as an inorganic iodide.

4. Considering the rate of accumulation, metabolization and excretion of 4-iodoalizarin 3-sulfonic acid, its application as a tracer for the study of physiologic or pathologic new bone formations was evaluated. It may be concluded that the application of the labeled dye as a tracer is impractical.

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THE EFFECTS OF ROENTGEN IRRADIATION ON ADRENAL CORTICAL FUNCTION IN MAN*

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IN 1954, a preliminary study by Soanes and Dodson[28] of a group of patients with testicular tumors suggested that some alteration of adrenal cortical function followed the administration of therapeutic doses of roentgen rays to the abdomen. The results of these studies, though inconclusive, raised the interesting question of whether transient or permanent adrenal cortical alteration occurred following such therapy to the region of the adrenal glands. Previous workers[2,4,21,23] have shown that with very large doses of roentgen rays there are morphologic changes demonstrable in the adrenal cortex. Aside, however, from the depletion of the sudanophilic substance[21] the dosage used to produce such changes has been far above that used for diagnostic or therapeutic purposes in humans. Alterations in adrenal function, resembling adrenal cortical insufficiency, have also been reported by a number of investigators,[7,17,23] but case histories of most of these patients again raise a question as to possible extrinsic complicating factors and the effect of the very high doses of radiation used. Desjardins,[2] after reviewing the experimental aspects of the subject, concluded in 1928 that, in spite of the morphologic disturbances in the adrenal cortex which may be produced by roentgen irradiation, the health of the animals did not appear to be deleteriously influenced. He, therefore, assumed that the adrenal gland was relatively resistant to radiation as compared with other organs of the body. Desjardins and Marquis[3] showed that 55 patients with apparently normal adrenal glands failed to reveal manifestations of adrenal insufficiency following therapeutic doses of roentgen radiation. Most of their work, however, was directed primarily at measuring what is now known to be medullary rather than cortical function, and the methods of study of true cortical function were very crude.

Lawrence,[8] using minimal lethal doses of total body roentgen irradiation on dogs, showed that there was a significant increase in steroid excretion several days following irradiation, and that the values then fell to normal or subnormal levels with a gradual return to normal. Rosenfeld *et al.*[16,22] noted a decreased secretion of hydrocortisone, cortisone, and other steroids by isolated calf adrenals which were perfused with ACTH-containing blood and exposed to Co^{60} irradiation. Patt *et al.*[10] observed a marked increase in adrenal weight and a decrease in adrenal cholesterol content following whole body roentgen irradiation of rats at levels of 650 r (LD_{50}) and 900 r (LD_{100}). After a whole body dose of 200 r (sublethal), however, there was little change. Leblond and Segal[9] have reported that adrenal hypertrophy occurs as a secondary response to roentgen irradiation of other portions of the body, but several early observers[2,6,13] found no such effect after direct irradiation of the adrenals. It should be noted that most of the early investigations pertained to humans and were rather poorly documented with animal experimentation, utilizing excessively large dosages, and generally whole body irradiation. The problem encountered in the human subject undergoing roentgen

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therapy is one of large but localized doses of radiation, which may or may not directly strike the adrenal glands.

It was, therefore, decided to study the adrenal function of a group of patients with testicular tumors to whom therapeutic doses of roentgen rays were administered through abdominal portals which included the region of both adrenal glands. This paper presents the findings of this study and discusses their significance.

MATERIAL

The 9 patients selected for this study ranged in age from twenty to forty-one years and all were Caucasian. They are listed in Table I, together with their diagnoses and the results of a six to seven year

Table I

DIAGNOSIS, TREATMENT AND FOLLOW-UP OF PATIENTS

Case	Age at Surgery	Surgery	Pathologic Diagnosis	Follow-up
1	22	Right orchiectomy	Seminoma	Living and well, 75 mo.
		Right inguinal lymph node biopsy	No significant pathologic changes	
2	26	Right orchiectomy	Seminoma with vascular invasion and interstitial cell hyperplasia	Living and well, 73 mo.
3	41	Right orchiectomy	Seminoma	Living and well, 72 mo.
4	39	Left orchiectomy	Seminoma with invasion of spermatic vein	Living and well, 68 mo.
		Excision of breast tissue, bilateral	Gynecomastia	
5	22	Right orchiectomy	Embryonal carcinoma	Living and well, 66 mo.
6	20	Right orchiectomy	Teratoma with embryonal carcinoma	Histologically benign teratoma, left supraclavicular region 5 mo. later—no other tumors; living and well, 71 mo.
		Right retroperitoneal lymph node dissection	No significant pathologic change	
7	40	Right orchiectomy	Embryonal carcinoma	Died of pneumonia, no tumor recurrence in 80 mo.
		Right radical retroperitoneal lymph node resection	Reactive hyperplasia	
8	21	Left orchiectomy	Teratoma with embryonal carcinoma	Died with generalized metastases in 7 mo.
		Retroperitoneal lymph node dissection	Retroperitoneal metastases	
9	20	Left orchiectomy	Teratoma with embryonal carcinoma and choriocarcinoma	Living and well, 66 mo.

clinical follow-up. All had testicular tumors which were surgically removed. At the time of surgery none of the patients showed evidence of renal or adrenal metastases, and only one showed evidence of low retroperitoneal metastases. Two, however, had vascular invasion in the spermatic cord. The pathologic specimens of these patients were examined independently by 4 pathologists and the diagnoses were reviewed and concurred in by the Armed Forces Institute of Pathology.

The purpose of the study was thoroughly explained to all patients and it was felt that they understood the necessity of complete cooperation, and all volunteered to participate. Insofar as possible, checks were maintained by nursing and medical personnel on the collection of the urine specimens. In almost all cases the 24-hour urine volumes were reasonable, and 24-hour creatinine excretion studies confirmed that complete 24-hour urine specimens were obtained.

METHOD

Surgical orchiectomy was performed by the usual procedure, and in the cases indicated (Table I) retroperitoneal lymph node dissection was also done. Postoperatively the adrenal glands were anatomically defined, using the upper poles of the kidney shadows on a flat roentgenogram of the abdomen as a guide for their location. It was felt that in all of the patients the adrenal glands were located with certainty. The perimeters of each patient's prescribed portals for radiation therapy were then outlined on the skin with lead markers and a flat roentgenogram of the abdomen was taken to ensure that the renal shadows were within the confines of the portals, and thus that the adrenal glands were within the field of direct irradiation. Treatment was then administered with the specific factors, dosage schedules, and relatively large portals indicated in Table II and Figures 1 through 4. It should be noted that in Case 7 the adrenal glands probably did not lie entirely within the direct projections of either the abdominal or epigastric portals. The right adrenal gland was almost completely within the epigastric portals and the left partially so. Both were immediately adjacent to the superior edge of the abdominal portals. In Case 9 a 15×7 cm. lead plate was placed over the epigastrium on the days indicated (Fig. 4) to protect the adrenal glands from direct irradiation.

Twenty-four hour urine specimens were collected in chemically clean bottles containing a few crystals of thymol as a preservative. The specimens were refrigerated throughout the period of collection, and then transferred to a deep freeze at a temperature of approximately $-5°$ C. and kept for analysis. The 17-ketosteroid excretion was determined by the method of Robbie and Gibson,[15] and the 17-hydroxycorticosteroids were determined by the Porter-Silber[11] method as modified by Reddy *et al.*[12] Adrenal cortical function was evaluated by the method described by Renold *et al.*[14] except that 40 international units of adrenocorticotrophic hormone (ACTH) were administered by continuous intravenous drip over a ten hour period. In a few instances the two day ACTH test of Thorn *et al.*[20] was used to obtain the additive effect of 40 international units of ACTH similarly administered on two consecutive days.

Almost daily 24-hour urine collections were made from the beginning of the control period throughout the course of irradiation and for a short period following cessation of irradiation. Intermittent follow-up studies were performed during the ensuing ninety days, as the patients were available. ACTH stimulation studies were performed on the days indicated in the respective figures. All collected urine specimens were analyzed for the 24-hour excretion of 17-ketosteroids, and selected specimens were analyzed for 17-hydroxycorticosteroids in Cases 3 through 9, since the 17-hydroxycorticosteroid analyses did not become available until the 40th day of the study of Case 3. In each case the patient acted as his own steroid excretion control (except 17-hydroxycorticosteroid excretion in Case 3).

TABLE II

ROENTGEN THERAPY OF PATIENTS

Case	Portals and Size (cm.)*	Duration (days)	Distance Skin to Depth (cm.)	Per Cent Depth Dose	Tissue Dose (r)* Daily	Tissue Dose (r)* Total	Total Adrenal Dose (r)
1	Opposing posteroanterior and anteroposterior abdomen 15×30	31	9.5	72	54/108	2,592	2,592
2	Opposing posteroanterior and anteroposterior abdomen 15×30	35	9.0	75	74/112	2,607	2,607
3	Opposing posteroanterior and anteroposterior abdomen 15×30	29	9.0	75	56/150	2,512	2,512
4	Opposing posteroanterior and anteroposterior abdomen 15×30	28	9.0	75	75/150	2,569	1,569
5	Opposing posteroanterior and anteroposterior abdomen 15×30	35	9.5	72	72/144	3,420	3,420
6	Opposing posteroanterior and anteroposterior abdomen 15×30	37	7.5	86	65/129	3,526	3,526
7	Opposing posteroanterior and anteroposterior abdomen 20×20	39	10.0	64	64/128	3,392	0†
	Opposing posteroanterior and anteroposterior epigastrium 12×12	35	10.5	48	72/120	3,216	3,216†
	Right lateral abdomen 10×10	1	15.0	27	81	81	0
8	Opposing posteroanterior and anteroposterior abdomen 18×30	36	8.5	78	59/156	3,510	3,510
	Opposing posteroanterior and anteroposterior mediastinum 10×20	30	8.5	66	66/132	2,904	0
9	Opposing posteroanterior and anteroposterior abdomen 15×7 (when not shielded)	37	10.5	64	32/128	2,112	2,112
	Opposing posteroanterior and anteroposterior abdomen 15×30 (with 15×7 shield part of time)	37	10.5	64	32/128	3,484	0

Note: In all cases a Maximar roentgen-ray machine was used with the following physical factors: 220 kv.; 0.5 mm. Cu, 1 mm. Al filter; 1.35 mm. Cu half value layer; 15 ma.; 70 cm. target source distance; 21.6 r/min. (air). In general, paired anteroposterior and posteroanterior corresponding treatment fields were irradiated on alternate days with no therapy on Sundays and holidays. Data on day to day treatment are detailed in Figures 1 through 4.

* For detailed locations of portals and record of daily treatments see Figures 1 through 4.

† In Case 7 the adrenal glands were not completely within the epigastric portals, and were very close to the abdominal portals.

In all cases, except Case 2, ACTH stimulation studies were done at or before the institution of radiation therapy; so again each patient acted as his own internal control.

RESULTS

The results of the steroid analyses on the 9 patients are summarized in Figures 1 through 4. These show the detailed day by day record of the 17-ketosteroid and 17-hydroxycorticosteroid excretion, and of the daily dose of radiation. For each patient or group of patients a sketch showing the detailed anatomic location of the portals used for irradiation is included. All steroid

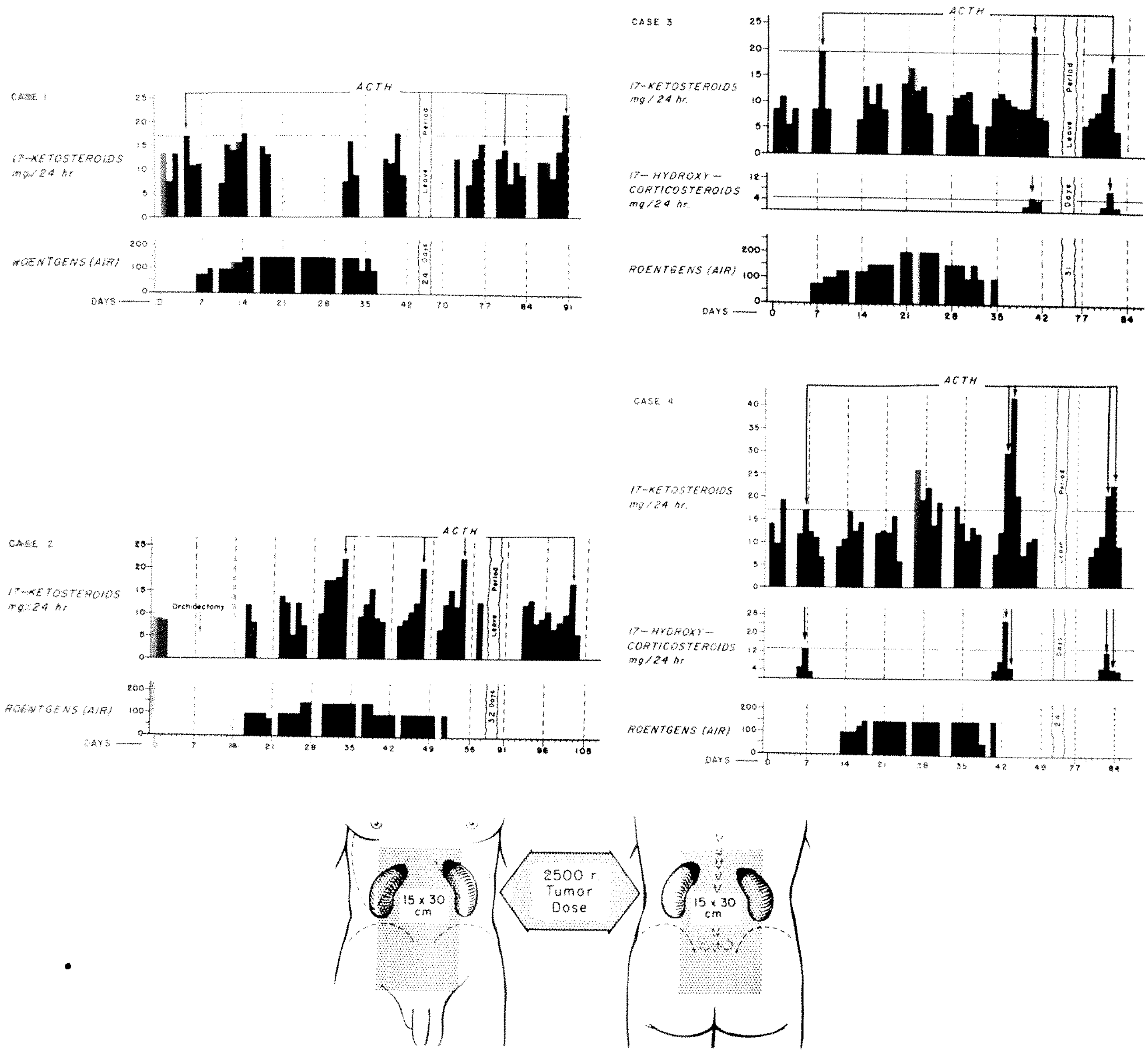

FIG. 1. Summary of irradiation portals and data of roentgen therapy and steroid excretion in Cases 1 through 4.

values are expressed in milligrams excreted in the urine for twenty-four hours. Days on which 40 international units of ACTH were administered intravenously to determine the effect of adrenal stimulation are indicated by arrows. The horizontal lines on the portions of the charts showing the steroid excretion indicate the level of steroid excretion on the first day of ACTH stimulation, prior to the commencement of irradiation. In some cases ACTH stimulation was done on two consecutive days but the steroid excretion level on the first day of stimulation was selected as the base line. Thorn *et al.*[20] have previously reported an additive effect of ACTH when administered on consecu-

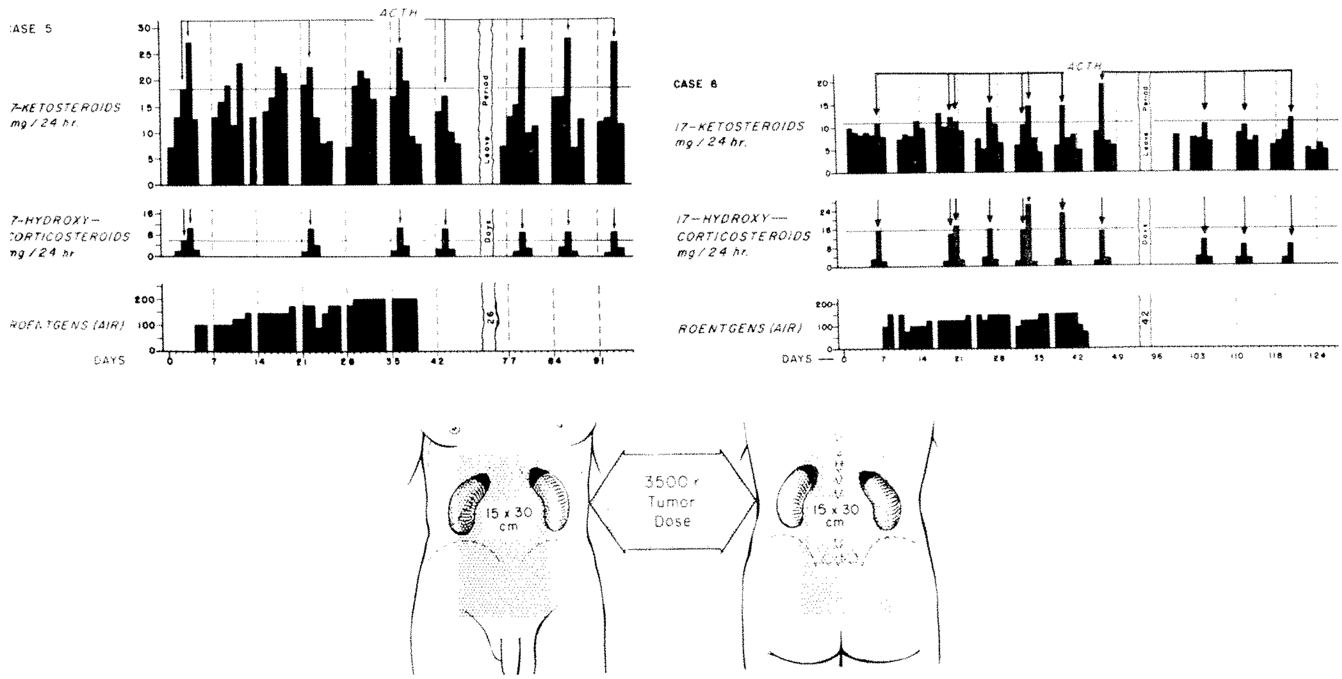

Fig. 2. Summary of irradiation portals and data of roentgen therapy and steroid excretion in Cases 5 and 6.

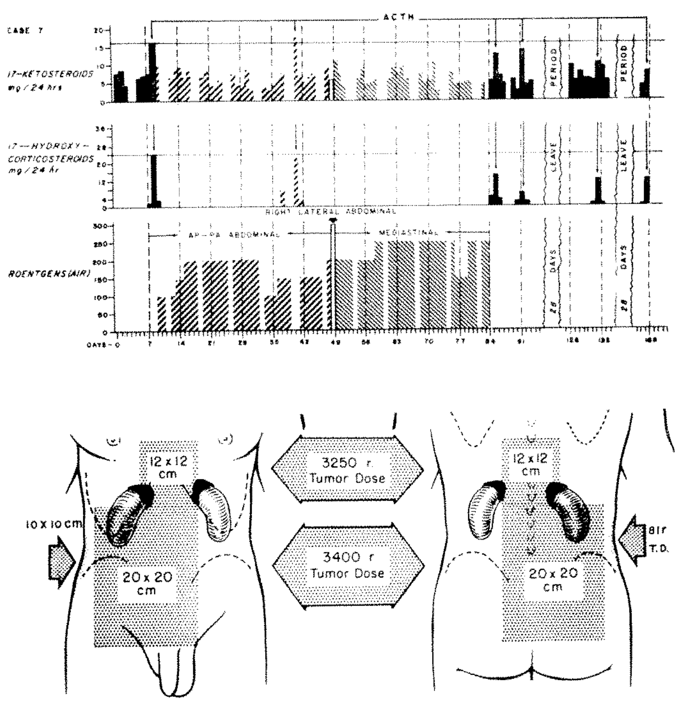

Fig. 3. Summary of irradiation portals and data of roentgen therapy and steroid excretion in Case 7.

tive days; therefore, it was felt that a more satisfactory and uniform base line stimulation level would be obtained by using the excretion level on the first day of stimulation.

Pre-irradiation 17 ketosteroid studies were carried out on each patient for several days. Examination of these values for each patient showed a marked day to day variation of the 24-hour urinary 17-ketosteroid excretion, with variations up to 100 per cent of the lowest value obtained. Such variations persisted throughout the period of observation, largely masking any actual change in adrenal cortical activity due to the irradiation. In most of the cases an intravenous ACTH stimulation study was done on or just prior to the first day of irradiation and repeated later in the course of therapy. Both 17-ketosteroid and 17-hydroxycorticosteroid analyses were carried out the day before, on the day or days of ACTH stimulation, and the day following. In the majority of patients the 17-ketosteroid excretion on the first day of ACTH stimulation was between 50 and 100 per cent higher than the highest nonstimulated value, but in Case 4 one of the control nonstimulation days gave a value that was higher than that on the first day of ACTH stimulation. In Cases 6 and 8 only a slight rise above the highest base line value was observed. The increase in 17-hydroxycorticosteroid excretion, however, was found to be much more pronounced, varying from a 100 to approximately a 400 per cent increase. From Figures 1 through 4 it is apparent that some trends in the 17-ketosteroid excretion values exist; however, the 17-hydroxycorticosteroid excretion determinations reveal these in a much more clear-cut manner. The marked day to day variations of the 17-ketosteroid excretion makes any interpretation of such data hazardous.

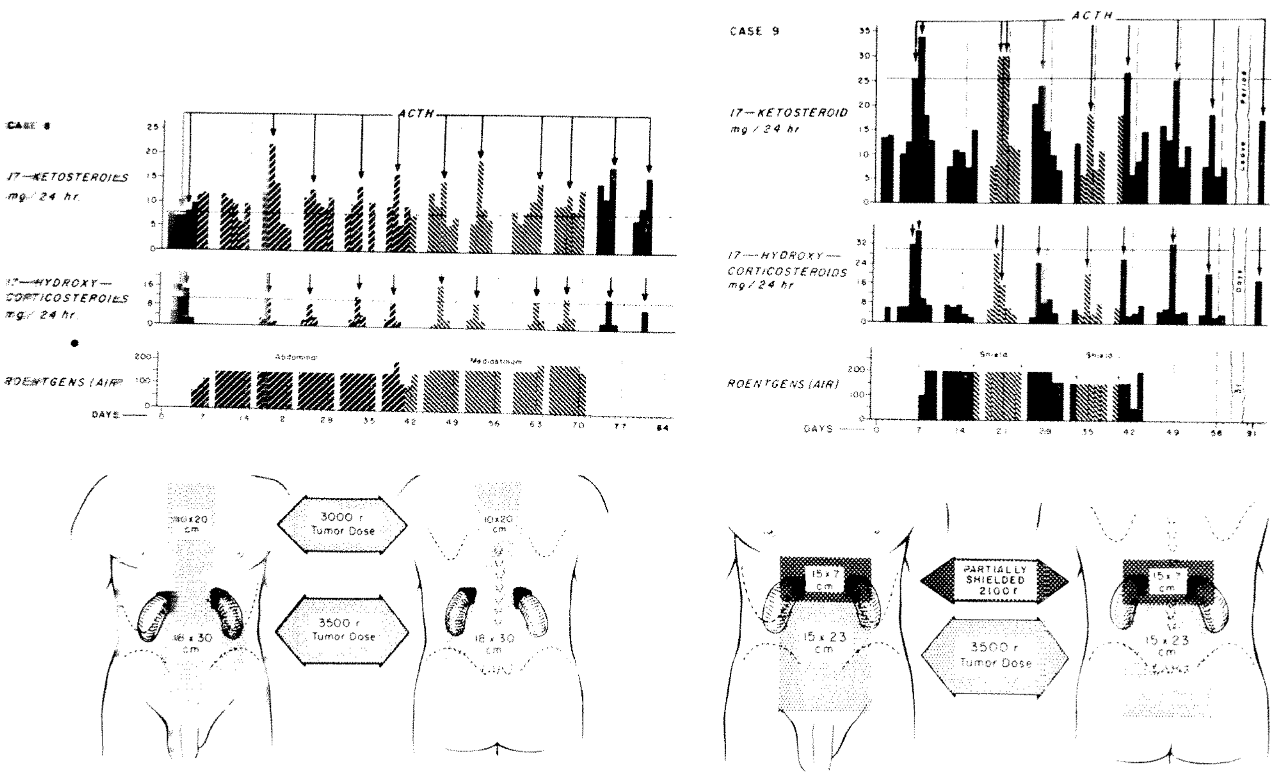

FIG. 4. Summary of irradiation portals and data of roentgen therapy and steroid excretion in Cases 8 and 9.

Where there are some differences in the excretory patterns of the two steroids, as in Cases 6, 7 and 8, it would appear that the 17-hydroxycorticosteroid data are those on which interpretations of adrenal cortical activity should be based.

The data in Figures 1 through 4 show a mild to moderate increase in 17-hydroxycorticoid excretion in response to intravenous ACTH stimulation during the latter part of radiation therapy and immediately following it, with a subsequent return to normal or below normal excretion levels. The increases range from an apparently insignificant amount in Cases 7, 8 and 9 to almost a 100 per cent increase in Cases 4 and 5. In some cases (especially in Cases 6, 7 and 9) a decrease in 17-hydroxycorticoid excretion in response to intravenous ACTH stimulation was observed late in or following the termination of radiation therapy. The two day ACTH stimulation tests revealed the expected increase in 17-hydroxycorticoid excretion on the second day of stimulation compared with the first, except in Cases 4 and 9 where after more than 2,000 r tissue dose of radiation to the adrenal glands the second day excretion value dropped off instead of rising. In Case 6 after 1,200 r, and again after 2,500 r, the second day excretion value was higher than that of the first day, as in the control tests.

Case 8 is the only patient in this series on whom autopsy material could be obtained. The autopsy revealed widely disseminated metastases of embryonal carcinoma of the testis with almost complete replacement of the left adrenal gland. The right adrenal gland, however, was not involved by tumor and careful study showed no significant histologic change. The patient was markedly cachectic at the time of death and Sudan IV stains of sections of the adrenal gland revealed a mild to moderate reduction of sudanophilic substance in the adrenal cortex, but the changes were consistent with the degree of cachexia and chronic illness of this patient. Hematoxylin and eosin, Masson trichrome, and reticulum stains revealed no evidence of any significant change in architecture and no increase in fibrous or reticular elements. The relative thicknesses of the zona glomerulosa, the zona fasciculata, and the zona reticularis were essentially normal. No evidence of significant vascular changes was found. Examination of sections of adrenal glands from other patients receiving large amounts of radiation to abdominal portals revealed no specific changes ascribable to the irradiation.

DISCUSSION

The steroid data clearly reveal the inadequacy of 17-ketosteroid excretion and the relative reliability of 17-hydroxycorticosteroid excretion in measuring adrenal cortical function. The effects of specific adrenal cortical stimulation are largely masked in many cases by the presence of considerable extra-adrenal 17-ketosteroid which is being simultaneously excreted. The 17-hydroxycorticosteroids are much closer metabolically to the adrenal cortex than the 17-ketosteroids, which may come from many different sources. The reasons for the excess extra-adrenal steroid are not apparent since all the patients are young men who have one testis and similar disease processes. It is interesting to note that in Case 9, which demonstrates very high unstimulated 17-ketosteroid excretion values, there is still a marked ACTH stimulation effect. This shows that the ACTH stimulation test is a measure of adrenal cortical reserve capacity.

Various previous workers[1,5,17,19] have shown that 17-ketosteroid excretion values rise for a short period during stress and then fall back to base line levels. These studies have been made largely in conjunction with trauma and disease, and such studies have not been reported in cases receiving roentgen irradiation. Selye[17] has proposed his theory of the "general adaptation syndrome" and the accompanying adrenal response to stress, which is consistent with the above observations. From the cases studied in this series, it is felt that prolonged irradiation represents severe stress, and in consonance with Selye's theory there

is an increased response of the adrenal cortex to intravenous ACTH stimulation. In most cases the steroid excretion values returned to approximately control levels in the period following cessation of irradiation. In some cases, however, an apparent permanent decrease in the capability of the adrenal gland to respond to intravenous ACTH stimulation after the delivery of larger therapeutic doses of radiation was noted. Since the adrenal glands of the one patient in this series who came to autopsy, as well as those of patients receiving similar high doses of roentgen radiation, showed no significant morphologic change, it is difficult to identify the exact pathologic process.

The most marked adrenal cortical impairment occurred in Cases 6 and 7, who received approximately 3,500 r tissue dose through portals encompassing the adrenal glands. Case 7 also received an additional 3,400 r tissue dose through other abdominal portals which did not include the adrenal glands. Although in this patient the adrenal glands were not completely within the field of either pair of anterior and posterior portals, they were largely included in the epigastric portals and very close to the superior margin of the abdominal portals, thus undoubtedly receiving a high dose of radiation. Adrenal cortical impairment occcurred without prior evidence of any significant enhancement of the adrenal cortical response to intravenous ACTH stimulation. It should be noted that relatively few 17-hydroxycorticosteroid analyses were made on this patient, and it is possible that some enhancement occurred but was missed. In Case 8 two separate pairs of portals (one abdominal pair including the adrenal glands and one mediastinal pair) were used, giving 3,500 r tissue dose to the adrenal glands. This patient showed a slight increase in adrenal cortical response to intravenous ACTH stimulation which persisted throughout therapy, but he was lost to steroid follow-up two weeks later. In Cases 1 through 6 only one pair of abdominal portals, which included the adrenal glands, was irradiated. Of these, Cases 4, 5 and 6 showed marked enhancement of adrenal cortical response to intravenous ACTH stimulation. Cases 5 and 6 received approximately 3,500 r tissue dose to the adrenal glands as compared to approximately 2,500 r in Cases 1 through 4. Case 6, however, was the only one of these patients to demonstrate subsequent adrenal cortical impairment.

The two day intravenous ACTH stimulation tests, performed prior to the beginning of irradiation, revealed a cumulative response to intravenous ACTH stimulation, as previously reported by Thorn *et al.*[20] Those performed late in the course of therapy, or following it, revealed an interesting pattern. In Case 4 after 2,500 r tissue dose to the adrenal glands, the 17-hydroxycorticosteroid excretion was markedly less on the second consecutive day of intravenous ACTH stimulation, and a similar effect was noted in Case 9 after approximately 2,000 r tissue dose of radiation to the adrenal glands. In Case 6 similar tests following tissue doses of approximately 1,200 r and 2,500 r did not show such a reversal. These data suggest that there may have been impairment of adrenal cortical reserve not manifested by the one day intravenous ACTH stimulation test. Thus, smaller doses of radiation (of the order of 2,000 r) than the 3,000–3,500 r necessary to manifest adrenal cortical damage by the one day intravenous ACTH test may reduce the ability of the organism to withstand stress situations. Further studies of this type with various adrenal and ACTH blocking substances would appear warranted to assess such lesser degrees of damage.

In an attempt to determine whether the alterations in adrenal cortical response were due to the direct effects of irradiation or to generalized toxic effects, regardless of whether the irradiation portals directly involved the adrenal glands or not, an attempt was made in Case 9 to alternately shield and irradiate the adrenals. Unfortunately, no significant enhancement effect

was encountered in this patient. During the second period of shielding, however, a drop in steroidogenesis in response to intravenous ACTH stimulation was noted, with a return to base line levels on redirect irradiation, followed by another drop after irradiation was completed. This is suggestive of an enhancement effect during direct irradiation of the adrenal glands rather than a systemic effect. It also suggests that the damage is the result of direct irradiation, becoming evident after cessation of the stimulatory effect during actual active irradiation, provided the dose has been large enough.

Cases 7 and 8 should cast some light on the problem of whether direct adrenal gland irradiation or generalized toxic effects are of more significance, since these patients received radiation therapy to portals including the adrenal glands and also to other portals. In Case 8 a 17-ketosteroid stimulation effect in response to intravenous ACTH was noted early during irradiation of portals including the adrenal glands, but only a transient true adrenal cortical stimulation as shown by the excretion of 17-hydroxycorticosteroids occurred. This was at the end and very shortly following the direct adrenal gland irradiation, occurring early in the irradiation of the mediastinal portals. In Case 7 little stimulation was noted, but insufficient analyses were performed. Definite adrenal cortical depression occurred late and persisted. Early stimulation and late depression were observed in Case 6 where only adrenal gland portals were irradiated.

It is felt that to obtain more significant data on this matter it would be necessary to study an additional series of patients receiving similar therapeutic doses of radiation to another area, for instance the chest, and then to compare them with Cases 1 through 6 in this series. The data obtained in this series, however, would appear to clearly indicate that enhancement does occur when the adrenal glands are directly irradiated. The data also suggest that the adrenal gland damage manifested by depressed steroidogenesis in response to intravenous ACTH stimulation is the result of such direct irradiation, generally following large doses.

The degree of response of the adrenal cortex to intravenous ACTH stimulation seems to be dependent on the tissue dose of radiation administered to the adrenal glands. Marked individual variation is apparent from this study. Tissue doses to the adrenal glands of approximately 2,500 r generally produce increased adrenal cortical activity in response to intravenous ACTH stimulation followed by a return to base line values with no subsequent impairment (Cases 1 through 4). Tissue doses of 3,500 r to the adrenal glands usually produce an initital stimulation followed by subsequent impairment as manifested by the *one* day intravenous ACTH stimulation test (Cases 5 through 8), while tissue doses of 2,000 to 3,000 r produce an initial stimulation with simultaneous impairment of the response to the *two* day intravenous ACTH stimulation test (Cases 4, 6 and 9).

SUMMARY

Nine cases of patients with testicular tumors receiving therapeutic doses of roentgen rays to the region of the adrenal glands are presented. The 17-ketosteroid and 17-hydroxycorticosteroid excretion studies were carried out prior to the initiation of radiation therapy, during therapy, and for a follow-up period. Adrenal steroidogenesis was evaluated by the response of the adrenal to stimulation with 40 units of ACTH administered intravenously over a ten hour period on one day, or on two successive days.

The data indicate a variable degree of enhancement of adrenal cortical steroidogenesis during or immediately following radiation therapy to the adrenal glands in the majority of patients, presumably reflecting the "general adaptation syndrome" to stress.[17] Most patients acquired a mild degree of adrenal cortical impairment secondary to such irradiation. The data indicate that the administration of more than

2,000 r tissue dose to the adrenal glands produces increased adrenal cortical steroidogenesis during irradiation in response to the *one* day intravenous ACTH stimulation test. Less than 2,000 r tissue dose produces no impairment or stimulation of adrenal steroidogenesis or reserve as measured by *one* or *two* day intravenous ACTH stimulation. Administration of 2,000–3,000 r tissue dose produces a transient stimulation with a simultaneous loss of adrenal cortical reserve as shown by intravenous ACTH administration on *two* consecutive days. More than 3,000 r tissue dose results in transient stimulation followed by subsequent adrenocortical impairment as manifested by stimulation by *one* day of intravenous ACTH administration. Following 3,500 r tumor dose, the adrenal glands still appear to have a normal amount of steroidogenesis under nonstress conditions, but their ability to respond to stress is markedly limited.

The data on patients receiving roentgen radiation through portals including the adrenal glands and through other portals suggest that the enhancement and impairment observed are both due to direct irradiation of the adrenal glands, but generalized secondary systemic toxicity may play a role. One patient who died showed no evidence of functional adrenal cortical impairment after 3,500 r tumor dose to the adrenal glands and 3,000 r tumor dose to the mediastinum. At autopsy, no histologic changes of the adrenal cortex were found. Study of the adrenal glands of other patients receiving similar doses of therapeutic roentgen radiation to the adrenal glands likewise failed to reveal any characteristic or significant histologic changes.

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SENSITIZATION AND RECOVERY PHENOMENA AFTER EMBRYONIC IRRADIATION*

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DURING the course of studies on the effects of radioactive phosphorus on the development of the rat embryo,[8,9] we found a much greater incidence of malformations when injection was made after six or after eight days of gestation than was expected on the basis of previous studies by Wilson et al.[10,11,12] They had noted that acute external roentgen irradiation of the rat embryo did not produce malformation when administered at eight days of gestation or before. Their experiments, among others, showed that a wide array of malformations which were largely characteristic of the age at the time of irradiation, could be produced by irradiation at nine days of gestation and therefter. Russell's[7] studies likewise demonstrated that irradiation during the comparable stages of development of the mouse did not induce anomalous development in this species. It was our first inclination to explain our findings on the basis of P^{32} remaining at nine days of gestation and thereafter. This was not possible, however, since we had found that too little radiophosphorus remained in this period to explain the incidence of malformation that was found.[9]

In searching for other possible explanations for this phenomenon, our attention was attracted to the recent revival of interest in the processes of recovery from radiation. In the use of fractionated radiations to determine the rate of recovery, two exposures are usually administered, an initial exposure followed by a second test dose. The first exposure is usually arbitrarily given as one half of the previously determined median lethal dose or LD_{50}. Implicit in this usage is the consideration that this initial increment of radiation would be without a grossly detectable effect, although it would of necessity have some effect which could be experimentally determined. This initial exposure may essentially be regarded as a sensitizing dose of radiation.

As early as 1920, a theory of recovery had been proposed by Kingery[4] according to which radiation produces some hypothetical decomposition product which in turn elicits clinical manifestations when present in sufficient concentration. He further postulated that recovery consisted of an exponential loss of this material. Although current concepts of radiation recovery do not require the presence of such a substance, an exponential recovery is commonly accepted. The so-called "Pfahler-Kingery" or "saturation" method of radiation therapy, which was proposed by Kingery[4] and expanded by Pfahler,[5,6] was based upon experimental and empirical estimates of these recovery times. This method consisted of fractionation with doses of decreasing size to establish and then maintain a plateau of effect. Recently, Du Sault[2] has proposed that a more careful study be made of fractionation effects to enable treatment planning to be derived more effectively, making use of the differential recovery rates which may be shown to occur between normal and neoplastic tissues in some cases.

These considerations have led us to experimentally examine the possibility that irradiation earlier in gestation might sensitize the embryo so that small amounts of radiation from P^{32} residual at nine or ten days of gestation would produce an effect greater than might otherwise be expected.

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MATERIAL AND METHODS

Virgin female rats of the Holtzman strain, weighing between 180 and 200 gm., were used in these experiments. These animals were caged nightly with males of the same strain and vaginal smears taken daily thereafter. Nine o'clock in the morning of the day on which the smear was found to contain sperm was considered to be the time of fertilization.

Groups of 10 to 12 pregnant animals were exposed to one of several doses of roentgen rays after six or after nine days of gestation. The animals were individually enclosed within segments of a lucite wheel-shaped device which rotated about the axis of the roentgen-ray beam. Exposure was made at 250 kv. peak with a G. E. Maximar machine. Operating this unit at 15 ma. with a parabolic aluminum field-flattening filter in addition to a 0.5 mm. copper and 1 mm. aluminum flat filter gave a beam of 1.75 mm. copper half value layer and a dose rate of approximately 16 r per minute.

From the examination of the resultant dose-response curves, which are shown in Figure 2, it was seen that treatment with doses of 110 r or less after six days of gestation did not increase post-implantation mortality above control levels. Neither this dose, nor even higher doses, produced any malformations when administered at this time of gestation. Accordingly, pregnant females were subjected to a sensitizing dose of 110 r at six days of gestation. They were again exposed three days later, at nine days of geststion, to a variety of roentgen-ray doses to establish the new dose-response curve.

In all cases, the female rats were sacrificed after fourteen days of gestation and the fetuses removed, weighed, and examined for gross malformations. The mortality percentage and weight depression at fourteen days of gestation were plotted against dose on probability graph paper and the ED_{50} determined by the method of Litchfield and Wilcoxon.[3] Similar functions were calculated for anomalous development in terms of the radiation dose which would produce a 50 per cent incidence of various specific gross abnormalities. For the purposes of this study, this was analyzed as the percentage of animals showing an arbitrary amount of decrease in the relative length of the mandible, reduction of the size of the external aspect of the eye, or failure of the processes composing the maxilla to close. The minimum extent of change that was denoted abnormal for the purposes of these calculations is demonstrated in Figure 1, *B* and *D*.

RESULTS

The 3 dose-mortality curves, in terms of the percentage of the embryos killed by fourteen days of gestation, are shown in Figure 2. It may be seen that these curves are essentially parallel to each other; this is confirmed by statistical analysis. Using the method of Litchfield and Wilcoxon,[3] an ED_{50} value of 178 r may be obtained for treatment at six days and 147 r at nine days of gestation; these differ significantly at the 95 per cent confidence level. When the pregnant females were given a preliminary exposure of 110 r at six days, only 115 r additional at nine days of gestation produced 50 per cent mortality by fourteen days. This displacement of the response curve by 32 r to the left implies that about 29 per cent of the six day exposure remains effective three days later for enhancement of the lethal effect.

Although all 3 curves have essentially the same general shape, there is a difference notable in terms of the apparent threshold, *i.e.*, the dose below which no effect is noted. It is seen that there is a distinct threshold of about 110 r or 80 r when irradiation was performed at either six or nine days of gestation, respectively. This threshold was not found when the exposure at nine days was preceded by a sensitizing exposure of 110 r at six days.

The corresponding curves for weight depression after irradiation at six or at nine days of gestation, which are not presented, show threshold values similar to those seen for mortality. The shapes are distinctly

Fig. 1. Gross anomalies used as criteria. (*A*) Profile of normal fourteen day rat embryo. (*B*) Profile of irradiated fourteen day rat embryo. Note decreased size of eye and nonclosure of maxillary processes. (*C*) Ventral aspect of head of normal fourteen day rat embryo. (*D*) Ventral aspect of head of irradiated fourteen day rat embryo showing shortened mandible.

different, however, in that they both plateau and are essentially horizontal over the upper dose range. The curve obtained with pretreatment at six days does not show such a threshold. Additionally, it has a lesser slope than the other 2 curves although it approaches the same maximum value of weight depression.

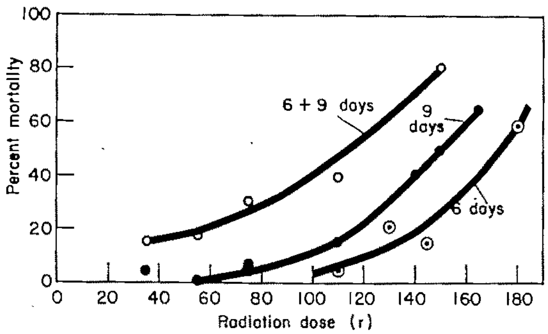

FIG. 2. Percentage mortality at fourteen days of gestation of embryonic rats after irradiation with various doses at six or nine days or pretreated at six days and again exposed at nine days of gestation.

As was indicated above, a reduction in the relative size of the mandible equal to or greater than that shown in Figure 1*D* has been considered anomalous. The percentage of fourteen day fetuses showing this amount of mandibular shortening has been plotted against dose in Figure 3.

At the levels of radiation used in this experiment, a 50 per cent incidence of mandibular shortening was not attained. The probit lines were extended and the ED_{50} values estimated; these were 180 r and 132 r for irradiation at nine days and for six plus nine days respectively. Because of this extrapolation as well as because the curves are not parallel over their entire length, the differences in ED_{50} cannot easily be tested by statistical means. It is further to be noted that the response curve associated with irradiation at nine days of gestation shows a threshold value of about 60 r, whereas there seems to be no threshold when a preliminary treatment is given three days earlier. Considering the curves only at the estimated ED_{50} level, there is a 48 r shift toward lower doses after a sensitizing exposure of 110 r at six days. This implies that 44 per cent of the earlier irradiation is effective after an interval of three days to enhance the effects of the second exposure.

The effects of this procedure have also been considered in terms of the percentage of fetuses showing microphthalmia somewhat less severe than that shown in Figure 1*B*. The two dose-response curves shown in Figure 4 are seen to have approximately the same shape. They may be shown to be parallel with greater than 95 per cent probability, although on inspection there seems to be a tendency toward increased slope for the curve resulting from preirradiation at six days. The ED_{50} of 93 r and 79 r for irradiation at nine or at six plus nine days, respectively, is significantly different at the 95 per cent confidence level. The curve obtained after a preliminary exposure at six days shows a 14 r displacement to the left. This would imply that only about 13 per cent of the first exposure remains effective for sensitization, which is somewhat less than that found for reduction in the size of the mandible. It is of interest to note, however, that the curves both show a threshold and that this, if it is shifted at all by the preliminary exposure at

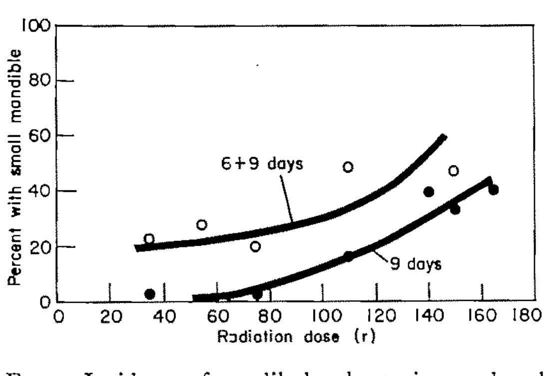

FIG. 3. Incidence of mandibular shortening produced by irradiation at nine days of gestation with and without pretreatment at six days.

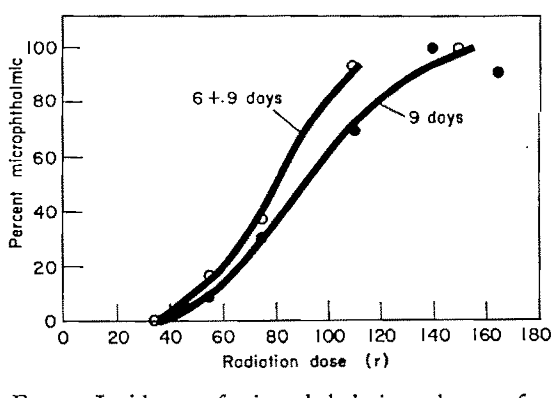

FIG. 4. Incidence of microphthalmic embryos after irradiation at nine days of gestation with and without pretreatment at six days.

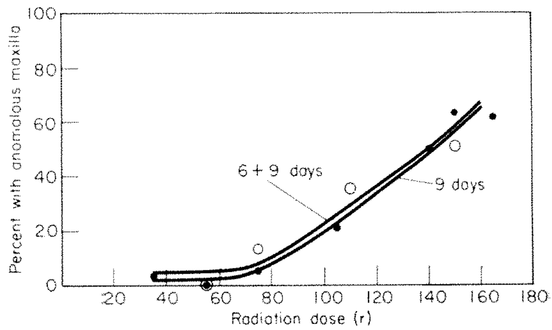

FIG. 5. Percentage of embryos with anomalies of maxillary development after irradiation at nine days of gestation with and without pretreatment at six days.

six days, is altered only by a very small amount.

The elements composing the maxilla are completely fused by the end of the fourteenth day of gestation in the normal fetus as shown in Figure 1, *A* and *C*. The degree of nonfusion indicated in this diagram was, for our purposes, considered to be anomalous. The curves of the percentage of fetuses showing this degree of incomplete fusion as a function of dose are shown in Figure 5. As will be noted, the slopes and ED_{50} are essentially the same whether or not a sensitizing exposure is given at six days. It would thus seem that treatment at six days does not influence the amount of maxillary damage produced by subsequent irradiation at nine days.

Abnormalities of the limbs, as well as malformations of the head such as microcephaly, blebs, and encephalocoele were seen in many of the fetuses. These anomalies were produced by lower doses of radiation when a sensitizing dose of 110 r was given at six days rather than when irradiation was administered at nine days alone. These changes were seen only at higher doses so that the data were insufficient to analyze quantitatively.

DISCUSSION

It is apparent from the results obtained in this experiment that an exposure to roentgen radiation at six days of gestation, which is itself without gross effect, potentiates the effect of a second exposure at nine days of gestation. On this basis it would seem that changes do occur in the six day embryo which are morphologically undetectable by usual techniques. These changes, which do not become apparent even at very high doses, remain for at least three days and are able to increase the magnitude of the response to additional radiation administered at that time. Since this effect is not detectable except through the use of additional radiation at some later time, it may be regarded as a sensitization process. The importance of this process, in terms of the production of certain malformations, is seen to be sufficiently great to account for the findings in our earlier experiments with radioactive phosphorus. It may thus be concluded that the small residual amounts of radioactivity remaining at nine days after injection of P^{32} at six days of gestation may be responsible for malformation production in an embryo sensitized by the earlier exposure.

It is not possible at this time to offer any explanation of the mechanisms involved in the sensitization to the production of malformations. This phenomenon poses less problems in terms of the lethal effect, since embryonic death can be produced by exposure at six days with doses slightly higher than those here used for sensitization. Although more detailed knowledge of the alterations leading to death would be required to decide whether or not the sensitization phenomenon was comparable to that operating in the case of the use of the divided dose technique for the study of recovery in the adult, it is felt that the two are akin.

The fact that the shift of the curves toward lower doses is in all cases less than the administered 110 r is of importance. When it is considered in the light of the uncertainty about the mechanisms involved, it gives rise to the possibility that recovery from the effect of the first radiation dose occurs in the three days between exposures. Insufficient information is available to choose between this possibility and

the alternative that the sensitization process is incomplete. If we assume a logarithmic relation for recovery from the lethal effects, as is found in the adult, the recovery rate may be quantitated. On this basis, a half-recovery time of 1.7 days would be obtained which is distinctly less than that found in the adult animal.

When this rate is compared with the series of recovery half-times for the lethal effect in adult animals, as presented in the review by Davidson,[1] relations of particular interest may be noted. He found, on compiling the available data, that recovery half-time was inversely proportional to the size of the animal. It is not known whether this is a phenomenon associated with size *per se*, since other parameters such as life expectancy, basal metabolic rate, and the average life of certain radiosensitive cells follow the same order within the series. Of importance, however, is the fact that we have obtained an estimated value of 1.7 days as the recovery half-time in the rat embryo, which is distinctly less than the range of values of three to eight days in the adult mouse and six to nine days in the adult rat. This presents the added possibility that recovery rate may also be related to the degree of differentiation of a tissue or to the general level of undifferentiated cells in an organism.

Clinically, it would be of certain great importance to know which of these possibilities are in fact responsible for the characteristic recovery rate. If it were to be found to be related to some one variable that could be manipulated under clinical conditions, it might be possible to increase the differential in recovery rate between normal and neoplastic tissue and thus effect more satisfactory radiation therapy.

The fact that a preliminary exposure at six days of gestation may produce a shift in the threshold or in the slope of a dose-response curve is of interest. There is the likelihood that such a relation of slope and threshold changes may pertain in the case of both normal and neoplastic tissues in the human. This would, of course, become most complicated in the case of multiple irradiations since it would imply a continuous change in these factors. Such a phenomenon would, however, have pronounced clinical value if it were definitely demonstrated to occur and was sufficiently well studied to be completely understood.

SUMMARY

Pregnant female rats were subjected to a preliminary exposure of roentgen rays at six days of gestation and again irradiated with a variety of doses at nine days. The results of such exposure, expressed in terms of embryonic mortality, growth, and abnormalities, were compared to the damage produced by a single exposure at either six or nine days.

It was found that a 110 r preliminary exposure dose reduced the LD_{50}, determined as the dose required to kill 50 per cent of the embryos by fourteen days of gestation, from 147 r to only 115 r. Pretreatment at six days with a second exposure at nine days also served to eliminate the threshold usually seen with single exposures from the dose-response curve. Similar results were obtained when weight depression was studied.

The dose of radiation at nine days of gestation required to obtain mandibular shortening in 50 per cent of the fetuses was markedly decreased by a previous exposure at six days. This treatment also significantly decreased the dose required to obtain eye changes. Pretreatment was not effective in increasing the incidence of maxillary changes.

The data obtained in these experiments have been interpreted as indicating that a sensitization of the embryo occurs which enhances the teratogenic effects of later radiation exposures. It was also found that recovery from certain of such effects may occur and at a rate greater than that found in the adult rat. These findings may be shown to have ultimate clinical importance.

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STRAY RADIATION FROM THERAPEUTIC ROENTGEN-RAY BEAMS*

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THE problem of radiation scattered to the side of a patient undergoing roentgen therapy may be of considerable importance when computing the protection requirements of a therapy room. Information about the quantity and quality of scattered radiation is available for the energy range 60 kv. to 100 kv.[1,6] and for Co^{60} radiation.[3] However, for the other energies, the convention normally adopted is that the scattered radiation measured at 1 meter from the scatterer does not exceed 0.1 per cent of the incident beam.[2,8]

In part A of this paper an experiment is described to test the validity of this contention for roentgen rays generated at voltages between 150 kv. and 250 kv. In part B an attempt is made on the basis of single scattering to account for the observed results.

(A) EXPERIMENTAL DETERMINATION OF SCATTERED RADIATION

EXPERIMENTAL ARRANGEMENTS

The experiments were performed by measuring the scattered dose at a point 40 cm. to one side of a phantom (Fig. 1). A water phantom 30 cm.×30 cm.×20 cm deep was irradiated by a beam of roentgen rays one edge of which was parallel to the side of the phantom. The distance from the target to the phantom surface was 50 cm. Most of the measurements were made with the edge of the beam coincident with the edge of the phantom; however, a shell of water of varying thickness was interposed between the edge of the beam and the edge of the phantom for part of the experiment to determine the shielding effect of the phantom material.

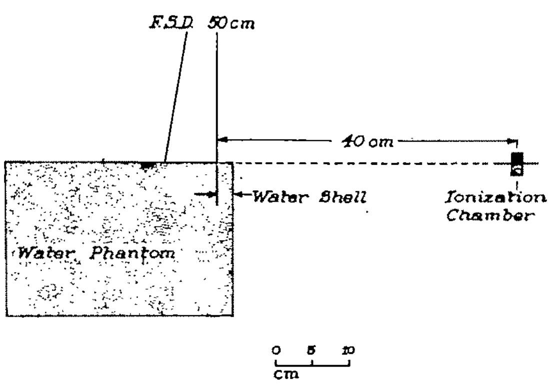

FIG. 1. Experimental arrangement illustrating the water shell.

In order to protect the measuring chamber* from the main beam, additional lead shielding was required around the tube head.

The experiments were carried out by exposing the surface of the phantom to 100 r incident air dose for various quality roentgen rays and measuring the amount of scattered radiation to one side of the phantom. This measurement was performed at 40 cm. for all experiments except one in which the dependence of scattered dose rate on distance was investigated by making the measurements at several distances from the edge of the phantom varying from 9 cm. to 56.4 cm.

Additional experiments were carried out to measure the variations in scattered dose as the field size was varied and also as the thickness of the water shell between the edge of the field and the edge of the phantom was varied.

RESULTS

The results of the experiments are shown

* The scattered dose was measured using ionization chambers of the M.R.C. design type B.D. 11, manufactured by the Baldwin Instrument Co. These chambers are stated by the manufacturer to be substantially independent of quality for gamma rays and all roentgen rays above 0.1 mm. Cu half value layer.

* From the Ontario Cancer Treatment and Research Foundation, Kingston Clinic, Kingston, Ontario, Canada. This paper was read, in part, at the Ninth International Congress of Radiology in Munich.

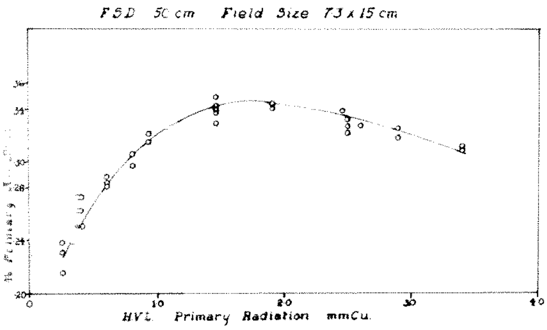

Fig. 2 Relation between the scattered dose, expressed as a per cent of the primary air dose, and the quality of the primary radiation.

in the following figures. Figure 2 shows the amount of scattered radiation 40 cm. to one side of the field in terms of per cent primary air dose for primary radiation of quality 0.35 mm. Cu to 3.40 mm. Cu. These results were obtained with no water shell between the edge of the beam and the ionization chamber. Figure 3 shows the variation in dose as a water shell is placed adjacent to the field edge in the path of the scattered radiation. From these graphs it may be seen that, at a position 40 cm. to one side of the scattering medium, the dose rate is approximately 0.3 per cent of the primary air dose rate. If a water shell of 10 cm. thickness is interposed between the edge of the field and the ionization chamber, one observes from Figure 3 that the dose rate is only reduced by a factor of one-half.

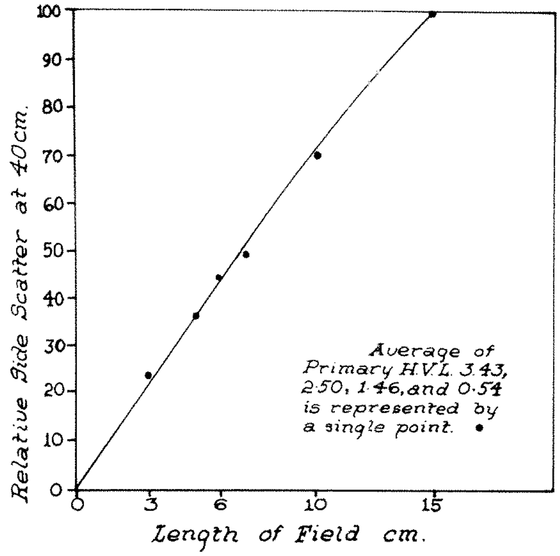

Fig. 4. Relation between side scatter and length of the field.

The results given above were obtained using a field area of 7.3 cm. × 15 cm. on the surface, the 15 cm. dimension being parallel to the phantom edge nearest the chamber. Figures 4 and 5 show the variation in scattered dose as the length and width of the field are varied. Figure 4 shows, as one would expect, that the amount of scatter to one side of a field varies almost directly with the length of the field, this relation falling off slightly for larger fields. The scattered dose also depends on the width of the field, as shown in Figure 5, but absorp-

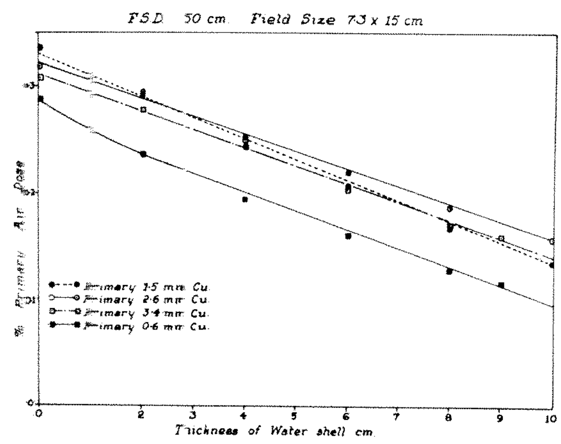

Fig. 3. Relation between side scatter and thickness of the water shell.

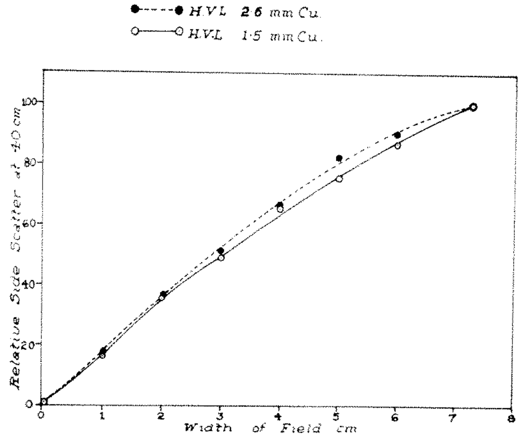

Fig. 5. Relation between side scatter and width of the field.

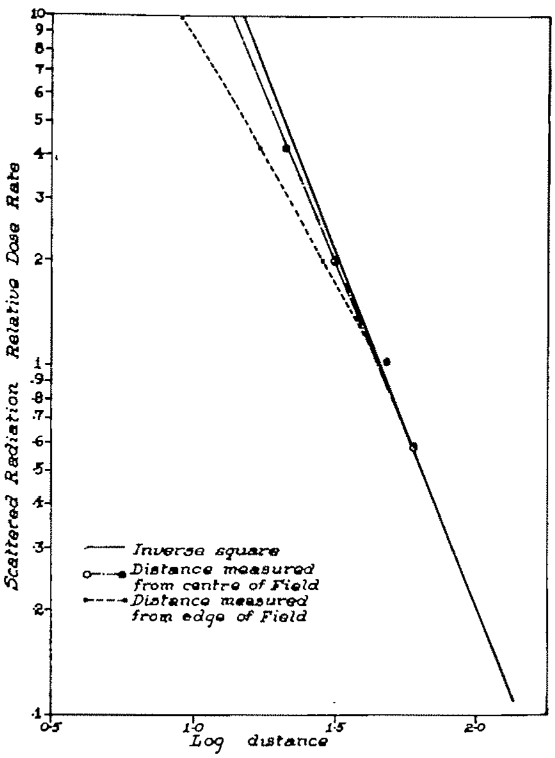

FIG. 6. Variation of side scatter with distance from the scattering medium.

tion in the phantom plays an increasing role as the width increases.

Measurements were made at various distances from the edge of the phantom in order to find whether the scattered dose rate did, in fact, fall off as the inverse square.

The results of this investigation are shown in Figure 6. The solid line in the figure denotes an inverse square relation. The middle curve shows experimental results when the distance was measured from the centre of the field; the lower curve gives the results when the distance was measured from the near edge of the field. It is seen from this figure that the variation in dose rate follows the inverse square law even down to the distances as short as 15 cm. from the centre of the field. The data for this curve were obtained using primary roentgen rays of qualities ranging from 0.54 mm. Cu to 3.4 mm. Cu half value layer.

Finally, an attempt was made to measure the quality of the scattered radiation. This was done by placing large sheets of copper over the side of the phantom and measuring the half value layer. While these measurements were not carried out using "good" geometry, they are at least an indication of the quality of the scattered radiation. The results of this investigation are shown in Figure 7. All primary beams with the exception of the 0.35 mm. Cu half value layer were produced by a roentgen-ray machine operating at 250 kv. The other point was obtained using roentgen rays generated at 150 kv. The points shown in Figure 7 were all measured with no water shell between the edge of the field and the edge of the phantom, with the exception of two points shown as solid circles for primary half value layers of 1.5 mm. Cu and 2.5 mm. Cu where additional measurements were made using a water shell 10 cm. thick. As seen from the graph, there was no significant change in the quality of the scattered radiation when this water shell was placed between the edge of the field and the ionization chamber. The half value layer of the scattered radiation, for the qualities investigated, is approximately one half of the primary radiation, tending to be harder than this at low energies and softer at high energies.

CONCLUSION

The conclusion which may be drawn from the results reported above is that, for roentgen-ray beams with a half value layer between 0.35 mm. Cu and 3.5 mm. Cu, the scattered dose one meter from the centre of

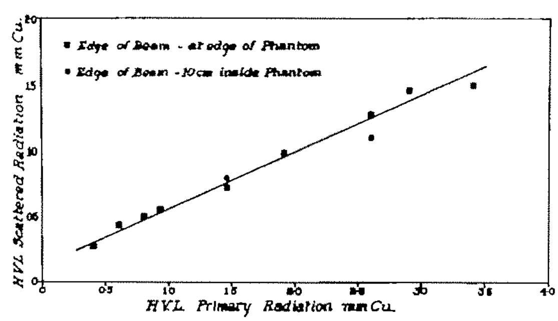

FIG. 7. The quality of the scattered radiation is plotted against that of the corresponding primary.

the beam and the patient, measured in a direction at right angles to the incident beam, is less than 0.1 per cent of the primary air dose delivered to the patient. The scattered dose was found to vary approximately as the area irradiated and the dose delivered to any point at right angles to the main beam will vary inversely as the square of the distance from the centre of the primary field to the point of measurement. Further, one may conclude that the half value layer of the scattered radiation is approximately one half that of the primary beam. As one would expect, the scattered radiation is somewhat softer at higher energies and harder at lower energies than the simple approximation referred to above. The quality of scattered radiation from a phantom irradiated by roentgen rays generated at 100 kv. peak (half value layer 0.8 mm. Al) was also investigated. Here the scattered radiation was found to have a quality of 4 mm. Al when an 8 cm. thick water shell was placed between the edge of the beam and the ionization chamber. This compares with a value of 2.9 mm. Al found by Keane and Spiegler[6] when the water shell was only 3 cm. thick.

(E) CALCULATION OF SCATTERED RADIATION

INTRODUCTION

Consider a parallel roentgen-ray beam $7\frac{1}{2}\times 15$ cm., instead of one diverging with focal source distance of 50 cm. as used in the experiment, impinging on the water phantom. This assumption should make little difference in the results. Consider also the single 90° scattering case as a first approximation (Fig. 8).

CALCULATION

Let D_λ be the dose rate at $P(x.y.)$ due to wave lengths between λ and $\lambda+d\lambda$ in the primary beam. Let the dose rate at P corresponding to D_λ in the absence of the phantom be $I_{0\lambda}$ r/min. Note that $I_{0\lambda}$ will not vary with x since we are considering a parallel beam.

Then $D_\lambda = I_{0\lambda}e^{-\mu x}$ where μ is the linear absorption coefficient for wave length λ.

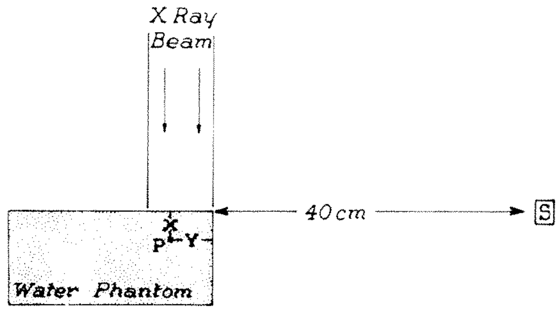

Fig. 8. Assumed geometry for theoretical consideration.

D_λ, however, is due to N_λ, the number of photons with wave length between λ and $\lambda+d\lambda$.

$$N_\lambda = \frac{10^9 \cdot D_\lambda E_\lambda}{1.6 \cdot 12.40/\lambda}$$
$$= 4.98 \times 10^7 D_\lambda E_\lambda \lambda \text{ photons cm.}^{-2}\text{sec.}^{-1}$$

where $E_\lambda{}^5$ is energy flux per roentgen for wave length λ and $d\lambda$ is measured in ångstroms. Now some of N_λ will be scattered through 90° and the number of these passing through each square centimeter at 40 cm. distance is:

$$N_{\lambda'} = N_\lambda n_0 \frac{d\sigma}{d\Omega} \frac{1}{(40+y)^2} e^{-\mu' y} dV,$$

where

$$dV = 15 \cdot dx \cdot dy.$$

n_0 is the number of electrons per gram for water phantom and μ' is the linear absorption coefficient for scattered radiation.

$d\sigma/d\Omega$ is the differential Klein-Nishina cross-section[7] for the number of photons scattered through 90° per unit solid angle per electron.

$\therefore$ Number of photons of wave length λ scattered through 90° and reaching S is $N_{s\lambda'}$

$$N_{s\lambda'} = \iint 4.98 \cdot 10^7 \cdot E_\lambda \lambda I_{0\lambda} e^{-\mu x} n_0 \frac{d\sigma}{d\Omega} \frac{15}{(40+y)^2} \cdot e^{-\mu' y} dx \cdot dy \text{ photons cm.}^{-2}\text{ sec.}^{-1}$$

where the primes refer to scattered radiation.

$\therefore$ Dose rate at S

TABLE I

μ'	$X \times 10^3$
.14	2.57
.17	2.34
.20	2.20
.25	1.91

$$S_{\lambda'} = \frac{N_{s\lambda'} \cdot 12.40/\lambda' \cdot 1.6 \cdot 10^{-9}}{E_{\lambda'}}$$

$$= 2.01 \cdot 10^{-8} \cdot \frac{N_{s\lambda'}}{\lambda' E_{\lambda'}} \text{ r/min.}$$

On substituting the appropriate values, this last equation reduces to:

$$S_{\lambda'} = I_{0\lambda} n_0 \frac{d\sigma}{d\Omega} \frac{\lambda}{\lambda'} \frac{E_\lambda}{E_{\lambda'}} \frac{15}{\mu} \int_0^{7.5} \frac{e^{-\mu' y}}{(40+y)^2} \cdot dy \text{ r/min.}$$

since $n_0 d\sigma/d\Omega$ is constant for a given wave length and angle of scatter. The remaining integral may be solved graphically. Calling this integral X, its value, found by graphical integration for various values of μ', is given in Table I.

Now let us use the above expression to calculate the spectrum (and amount) of scattered radiation from a phantom irradiated by 250 kv. (half value layer 2.6 mm. Cu) roentgen rays. The spectrum of the primary radiation as determined by Greening's method[4] is shown in Figure 9.

The values of $S_{\lambda'}$ versus λ' found by the calculation outlined above are also shown on Figure 9 with a dotted curve. Taking values from this graph, we may calculate the penetration through Cu filters of 0.5 mm., 1.0 mm., and 1.5 mm. thicknesses, respectively. These spectra lead to a calculated half value layer for the scattered radiation of 1.5 mm. Cu. Experimentally, the half value layer was found to be 1.2 mm. Cu. By experiment, the scattered dose rate at 40 cm. to one side of the field was 0.33 per cent of incident air dose, whereas the above calculation gives a figure of 0.16 per cent. The above calculations were repeated with two other spectra, and the results are summarized in Table II.

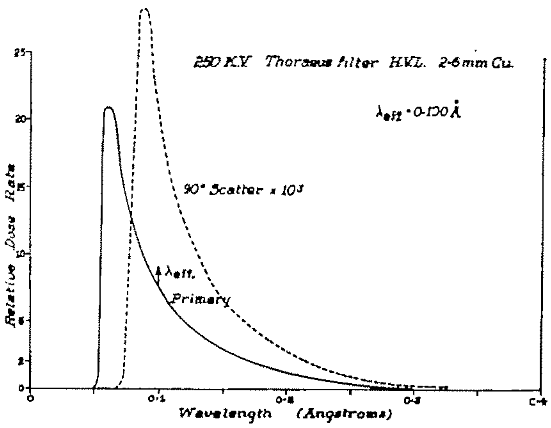

FIG. 9. Calculated primary and scattered spectra for 250 kv. roentgen rays.

The primary and secondary spectra for these two additional half value layers are shown in Figures 10 and 11, respectively.

CONCLUSION

The results of our simple single scattering theory are seen to be quite sufficient to

TABLE II

Primary Beam		90° Scattered Radiation			
kv.	Half value layer	Half value layer		Dose rate (per cent of primary)	
		Experimental	Calculated	Experimental	Calculated
250	2.6 mm. Cu	1.2 mm. Cu	1.5 mm. Cu	0.33	0.16
200	1.0 mm. Cu*	0.57 mm. Cu	0.65 mm. Cu	0.32	0.17
100	0.8 mm. Al	4.0 mm. Al†	2.7 mm. Al	0.05†	0.046

* 15 per cent characteristic radiation.
† This value was obtained with an intervening water shell 8 cm. thick and with a focal skin distance of 20 cm.

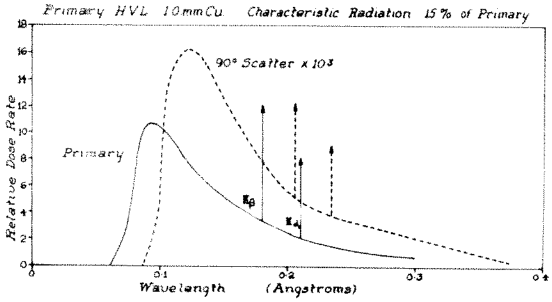

FIG. 10. Calculated primary and scattered spectra for 200 kv. peak roentgen rays.

explain the large differences in wave length of the primary and scattered radiation. Quantitatively, however, single scattering would appear to account for only about one-half of the total quantity of radiation which is scattered to a point to one side of the beam.

SUMMARY

The first part of this paper describes an experiment to measure the quantity and quality of radiation scattered through 90°

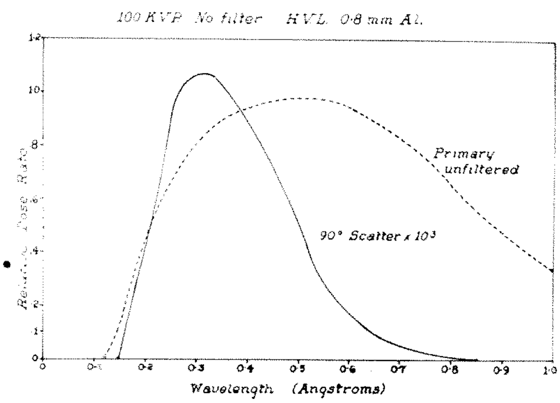

FIG. 11. Calculated primary and scattered spectra for 100 kv. peak roentgen rays.

from a water phantom, which was irradiated by incident radiation whose quality was varied from 0.35 mm. Cu to 3.4 mm. Cu. The shielding effects of a water shell between the edge of the beam and the edge of the phantom were investigated as well as the variation in scattered dose rate with field size and distance from the scattering material.

In the second part of the paper the quantity and quality of scattered radiation are calculated on the basis of single scattering only and the results of these calculations are compared with the experimental results obtained in the first part.

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ROENTGEN REGRESSION IN AXOLOTL (SIREDON MEXICANUM)*

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THIS study is a review of all data concerning the phenomenon of regression, resorption, or reduction, which was observed after local irradiation of young or adult axolotl in our various investigations. This phenomenon was first reported more than twenty years ago[5,6,8] and in the following years some new observations were made concerning this problem. In 1950 the reduction of connective tissue and pigment cells during the primary acute reaction in irradiated tail of young axolotl was described;[9] in 1952, the resorption of teeth in young axolotl;[16] in 1954, the reduction of pigment cells in the irradiated anterior portion of the head of young axolotl;[11] in 1958, the resorption of the lens in the eye of young axolotl;[15] and in 1959, the resorption of teeth in adult axolotl.[14] All these data are summarized in this paper along with some previously unpublished data.

Primarily, this paper reports an investigation of the most typical phenomena in the reaction of limb regenerates of adult axolotl to irradiation. This study is a repetition of earlier work and was done to verify our earlier conclusions concerning the resorption process.

MATERIALS AND METHODS

Forty-four adult axolotls, four to five years old, of different strains were used. The hind limbs of all animals were amputated in the femoral region. At the time of irradiation, 79 days later, the regenerated limbs were 9–12 mm. long and possessed 4 toes. The right hind limb regenerates of 22 animals were irradiated locally with 4,000 r and those of 12 animals with 6,000 r; the left hind limb regenerates served as nonirradiated controls. Ten animals served as additional untreated controls.

The irradiation was carried out at 100 kv., 30 ma., 1 mm. Al filter, beryllium window tube, half-value layer of 2.0 mm. Al, intensity of 410 r/min. in air, and a target object distance of 18 cm. Before irradiation the animals were anesthetized with a weak aqueous solution of tricaine methanesulfonate (M.S. 222) and then held in a coiled position by an elastic bandage so that only the right hind limb was free. The right hind limbs of 4 animals were irradiated simultaneously. The bodies of the animals were shielded with a 4 mm. lead sheet having a radiation localizer 6.5 cm. in diameter.[10] Immediately after treatment, the animals were put into water, where they recovered from the anesthesia. For histologic study, the limbs were fixed in acetic mercuric chloride formalin (Stieve). The material was embedded in paraffin with 5 per cent beeswax and sectioned at 8–10 microns. The sections were stained with Ehrlich's hematoxylin and eosin, and photomicrographs were taken of different areas at various magnifications.

THE NORMAL PROCESS OF REGENERATION

Among the Amphibia, the Urodela (newts, axolotls, salamanders, etc.) are able to restore limbs, tail, and parts of the head following injury or amputation. As soon as bleeding stops, the healing process begins. The initial epidermal healing of the wound is accomplished by a migration of epidermal cells or by migration of the epidermal layer from adjacent regions. This occurs without extensive mitotic activity (Korschelt, 1927). The healing of

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the wound is a separate process which is not related to the regenerative ability. In animals which possess the ability to regenerate, it is manifest only after the wound is completely healed. Regeneration begins only under suitable conditions; it cannot begin, for example, in the absence of a freshly healed wound.

The process of regeneration starts with resorption of the damaged tissue at the site of amputation. The giant wandering cells phagocytize all distal portions of the tissues, all damaged cells, dead blood cells, etc. Immediately thereafter, in the distal portion of the amputated limb, accumulated mesenchymal cells begin to divide rapidly, forming the anlage of the new regenerate, the regeneration blastema (Korschelt, 1927). After the regeneration blastema is formed, a period of more rapid regeneration with progressing tissue differentiation is observed. Usually, within two or three months after amputation, a full-sized limb with 5 digits is formed in adult newts (Triton cristatus) and in adult axolotls (Siredon mexicanum).[4] Regeneration is a rapid morphogenetic process and the missing organ may be restored in one-fourth or one-fifth of the time required for normal ontogenetic development.

RESULTS OF MICROSCOPIC INVESTIGATION OF TISSUES OF LIMB REGENERATES UNDERGOING REDUCTION

Thirty-three hind limb regenerates were studied histologically. Twenty had been irradiated with 4,000 r and 13 with 6,000 r. All conclusions concerning tissue damage and percentage frequency of tissue damage were derived from this material.

SKIN EPITHELIUM AND SUBCUTANEOUS PIGMENT LAYER

In general, changes in the skin epithelium are important for an evaluation of the irradiation effect.[12] During regression of the limb, the skin epithelium appeared greatly reduced. The surface area of epithelium of regenerates with 4 toes was many times greater before reduction than the corresponding surface area of the small remnants of regenerates without toes which remained after reduction. Gradual reduction of the skin epithelium without the formation of open wounds was typical. The reason for this reduction remains obscure.

The appearance of the skin epithelium depended upon the interval between irradiation and fixation. With early fixation (45–80 days after irradiation) epithelial damage was evident in 70 per cent of the animals irradiated with 4,000 r and in 80 per cent of those irradiated with 6,000 r. Typical epithelial damage was the formation of giant cell degenerating epithelium, usually observed during the primary acute reaction.[7,8,9,15] A comparison of such epithelium (Fig. 1, 3 and 4) with the normal epithelium of control animals (Fig. 2) showed that in irradiated epithelium the cells and nuclei were two or three times larger. Abnormal epithelium in some cases had irregular outer and inner surfaces and some of the epithelial giant cells were isolated from the epithelium and had penetrated into subepithelial loose connective tissue (Fig. 1). The number of cell layers was reduced in most cases. As a result, only one layer of giant cells (Fig. 3 and 39) or occasionally two layers of cells (Fig. 5) were seen. In comparatively rare cases, in spite of the giant size of the cells, the number of cell layers was almost normal (Fig. 4).

In 12 per cent of animals, fixed 124–126 days after irradiation, typical giant cell epithelium was observed (Fig. 1). In all other animals fixed at this time, the epithelium appeared normal and was indistinguishable from that of controls (Fig. 30, 31 and 37). This condition corresponded to the secondary stable state.[9,15]

Our earlier opinion that epithelial reduction occurs as a result of the activity of giant macrophages, which produce the lytic enzymes in immediate proximity to the epithelial cells, is not confirmed by the present investigation. In spite of active degeneration of the epithelial cells, macro-

phages were rarely found in their immediate proximity. Giant cells, similar to macrophages, were sometimes noted near the lower layer of epithelium (Fig. 15), but we consider these cells to be modified giant epithelial cells, distinguishable from the typical macrophage (Fig. 14). Macrophages, on the contrary, were found near completely normal epithelium. Reduction of epithelium did not appear to depend upon the general process of resorption of the limb.

The number of pigment cells in normal skin varies. Separate pigment cells (Fig. 31) are sometimes found in either continuous subepithelial pigment layer. After irradiation, pigment cells were damaged in all cases; however, the degree of damage varied considerably. In rare instances the pigment cells disappeared completely (Fig. 37); in most there were isolated normal pigment cells (Fig. 30) and damaged cells without processes (globular form) nearby. The condition of the pigment cells did not depend upon the condition of the adjacent tissue. Normal pigment cells were found under degenerating giant cell epithelium and damaged cells under normal epithelium. The reaction of the pigment layer to irradiation may, like that of epithelium, be independent of the general process of limb reduction.

SKELETON

I. *Resorption of the Skeleton of Adult Animal.* After irradiation with 4,000 r, resorption of skeletal cartilage and bone was observed in 80 per cent of the animals with early fixation and in 100 per cent of the animals fixed 124–126 days later. After irradiation with 6,000 r, resorption of the skeleton was observed in 100 per cent of the animals at either time. This investigation confirmed our previous conclusions[4,8] that resorption of the limb skeleton is the result of the activity of macrophages.

In regenerates with four toes, which were studied in this investigation, a comparatively thin layer of bone usually covered both the proximal and distal portions of the cartilaginous skeletal element (Fig. 11). Sometimes, however, it covered only the proximal portion (Fig. 6) or the distal portion (Fig. 11). The attack of macrophages on the skeletal element always began at the surface and often at the distal or proximal end. Therefore, in most cases the peripheral bone layer was damaged first.

Plate I.

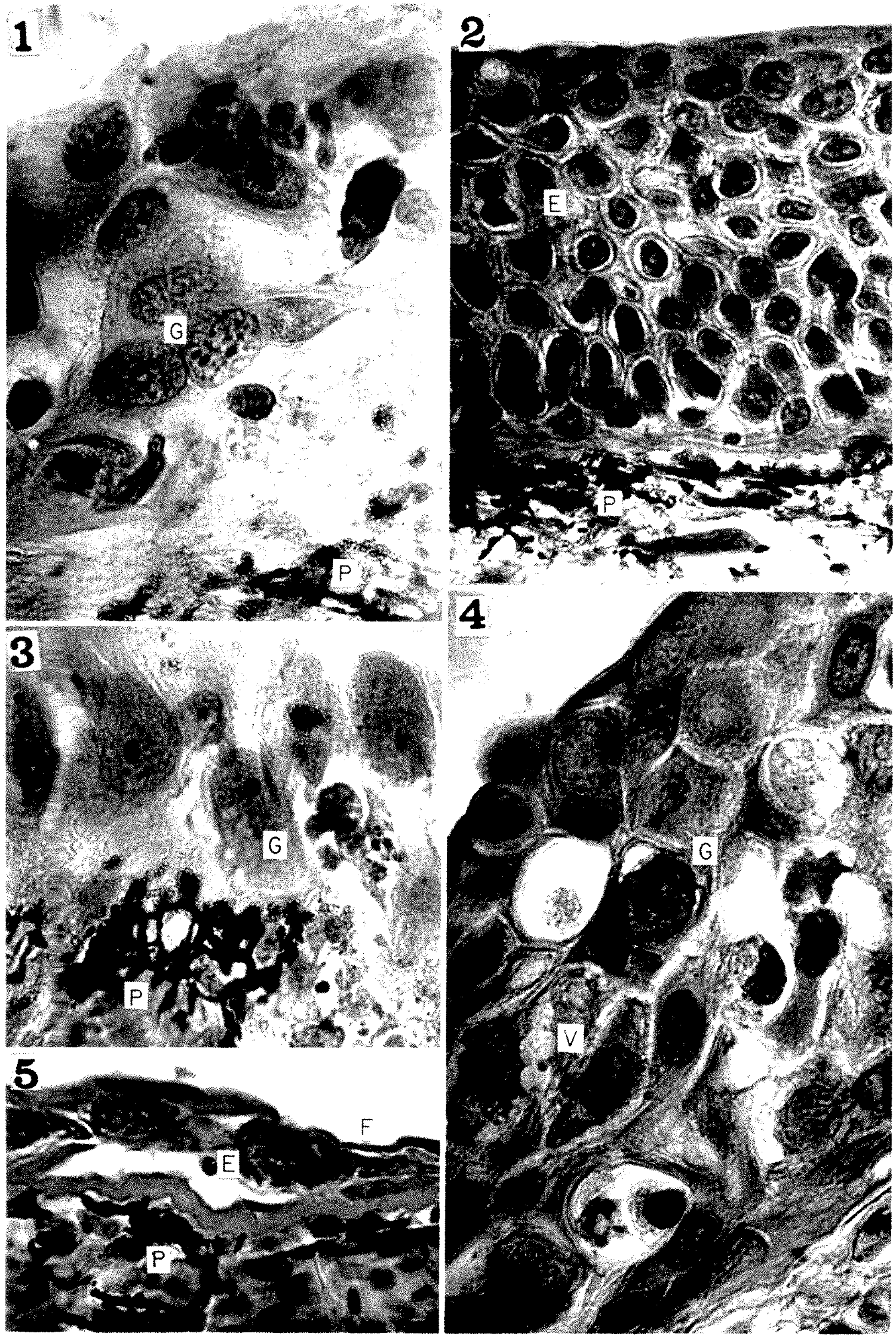
Fig. 1. Limb regenerate of axolotl (No. 16) 126 days after local irradiation with 4,000 r, showing abnormal skin epithelium. G—giant epithelium cells; P—pigment cells. Photomicrograph ×500.

Fig. 2. Limb regenerate of a control animal. E—normal epithelium cells; P—pigment cells. Photomicrograph ×500.

Fig. 3. Limb regenerate of axolotl (No. 17) 63 days after local irradiation with 4,000 r, showing abnormal skin epithelium. G—giant epithelium cells; P—pigment cells. Photomicrograph ×500.

Fig. 4. Limb regenerate of axolotl (No. 27) 63 days after local irradiation with 4,000 r, showing abnormal skin epithelium of great thickness. G—giant epithelium cells; V—vacuoles in protoplasm of epithelial cells. Photomicrograph ×500.

Fig. 5. Limb regenerate of axolotl (No. 12) 64 days after local irradiation with 4,000 r, showing abnormal epithelium consisting of only two layers of cells. E—lower layer of giant cells; F—exterior layer of flat cells; P—pigment cell. Photomicrograph ×500.


1
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The degree of damage depended on the number and size of macrophages accumulated in any particular area. In some cases, many macrophages were crowded in one place and the bone layer was completely destroyed on one side, but hardly damaged on the other (Fig. 6 and 7). In exceptional cases the bone layer disappeared completely in the early stages of skeletal resorption. Wherever there was bone or cartilage damage, macrophages were located in close proximity to the bone surface (Fig. 7 and 8). The cavities and holes in the bone or cartilage resulted from the action of lytic enzymes secreted by macrophages (Fig. 6 and 9). In some cases the exterior bone layer was only partially damaged. After a hole was formed in the bone layer, macrophages were able to penetrate into the cartilage. In such cases the bone layer temporarily remained almost intact, having only a few small cavities (Fig. 10), while almost all the cartilage within was dissolved. Apparently, the intercellular substance of cartilage was rapidly dissolved by macrophage enzymes. As a result, in some cases (Fig. 10) most of this substance disappeared, leaving isolated cartilage cells with large macrophages between them. Through phagocytosis, apparently, engulfed cartilage cells appeared within the macrophages as inclusions (Fig. 10). In some cases the distal skeletal elements were normal (Fig. 12), while the more proximal elements were undergoing reduction (Fig. 13). In the early stages of reduction, only a few macrophages were attached to the surface of the cartilage element, which was practically undamaged (Fig. 6). The appearance of skeletal cartilage undergoing reduction (Fig. 10 and 13) was in great contrast to that of the normal cartilage of a control animal or the undamaged cartilage of the same animal (Fig. 11 and 12). In cartilage undergoing reduction, the number of cartilage cells was greatly decreased (Fig. 13 and 20). Probably most of these cells were phagocytized by macrophages, since macrophages were typically present in close contact with the cartilage and penetrating into it (Fig. 13 and 20). The marcophages varied in size and activity. Giant macrophages were comparatively rare and never penetrated deeply into the cartilage element. These macrophages and those of medium size were the most active phagocytes. The smallest macrophages, only three or four times larger than carti-

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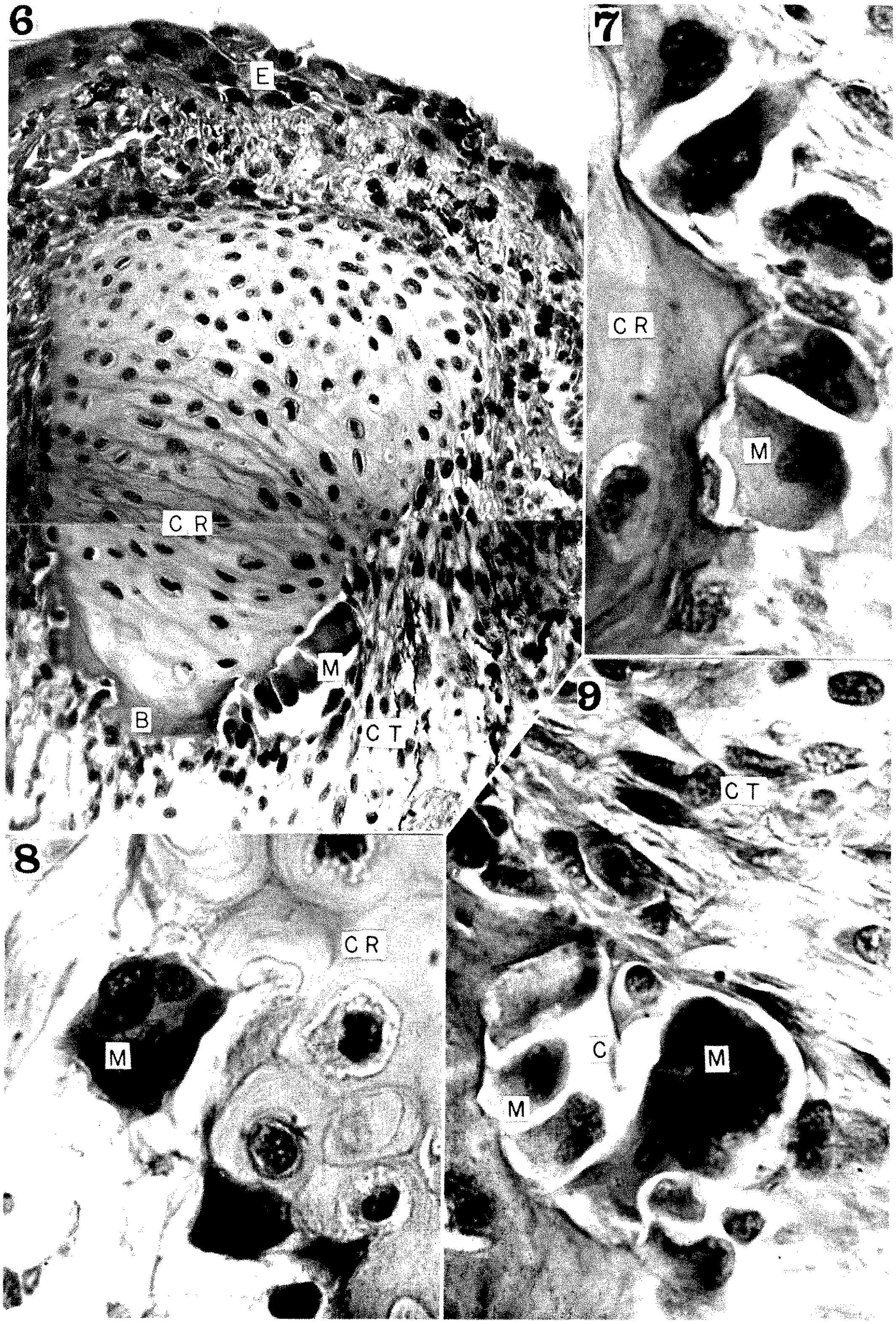
PLATE II.

FIG. 6. Limb regenerate of axolotl (No. 27) 63 days after local irradiation with 4,000 r, showing the beginning of reduction of the skeletal element. B—proximal layer of bone damaged in several places by macrophages; CR—cartilaginous tissue of skeletal element; CT—loose connective tissue; E—skin epithelium; M—macrophages, which have dissolved the bone layer and are starting to penetrate into cartilage. Photomicrograph ×150.

FIG. 7. Part of the section through the limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. CR—cartilage; M—macrophages. Photomicrograph ×500.

FIG. 8. Limb regenerate of axolotl (No. 27) 63 days after local irradiation with 4,000 r. CR—cartilage; M—macrophages. Photomicrograph ×500.

FIG. 9. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. C—cavity formed in cartilage by macrophages; CT—connective tissue cells; M—macrophages. Photomicrograph ×500.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lage cells, penetrated deeply into the cartilage substance. They actively dissolved cartilage, because they were always located in the empty spaces formed in the skeletal element (Fig. 18). In other cases, small cavities were connected and transformed into one large cavity occupying almost the whole cartilage element (Fig. 13). Such spaces were never seen in normal cartilage tissue (Fig. 12 and 19). In some cases a few large macrophages penetrated into the cartilage, but they were almost inactive, because the cartilage was not dissolved and typical cavities were not found (Fig. 16 and 17). Resorption was not continuous in all cases; however, the cause of its interruption is not known. When resorption was complete, all macrophages disappeared.

II. *Resorption of the Skeleton of Young Animals.* In recent experiments (Brunst—unpublished), the posterior portions of the body of young axolotls were irradiated with 1,000 r 50 days after hatching. About two months later the tails and hind limbs of most animals were distinctly reduced. Histologic investigation of an animal fixed 130 days after irradiation showed clearly the destructive activity of macrophages in the tail undergoing reduction. Many of these giant cells were in close contact with various bone portions of the vertebrae (Fig. 22).

Under higher magnification, macrophages were seen penetrating the bone (Fig. 21, 24 and 25) and attached to the bone surface (Fig. 23). The bone substance was dissolved and a large cavity had formed in the bone (Fig. 21, 24 and 25), apparently as a result of the activity of lytic enzymes produced by the macrophages. The shape of the bone cavity often corresponded to that of the macrophages (Fig. 21 and 25), suggesting that such a cavity was formed under the influence of macrophage processes which produced the lytic enzyme. Many protoplasmic inclusions, either

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PLATE III.

FIG. 10. Limb regenerate of axolotl (No. 27) 63 days after local irradiation with 4,000 r. B—exterior bone layer partially damaged by macrophages; C—cavity in bone layer, formed as a result of macrophage activity; CI—isolated cartilaginous nuclei left after both intercellular and intracellular substance have been dissolved; CR—cartilage, almost normal in appearance; H—hole in bone layer; M—macrophages. Photomicrograph ×150.

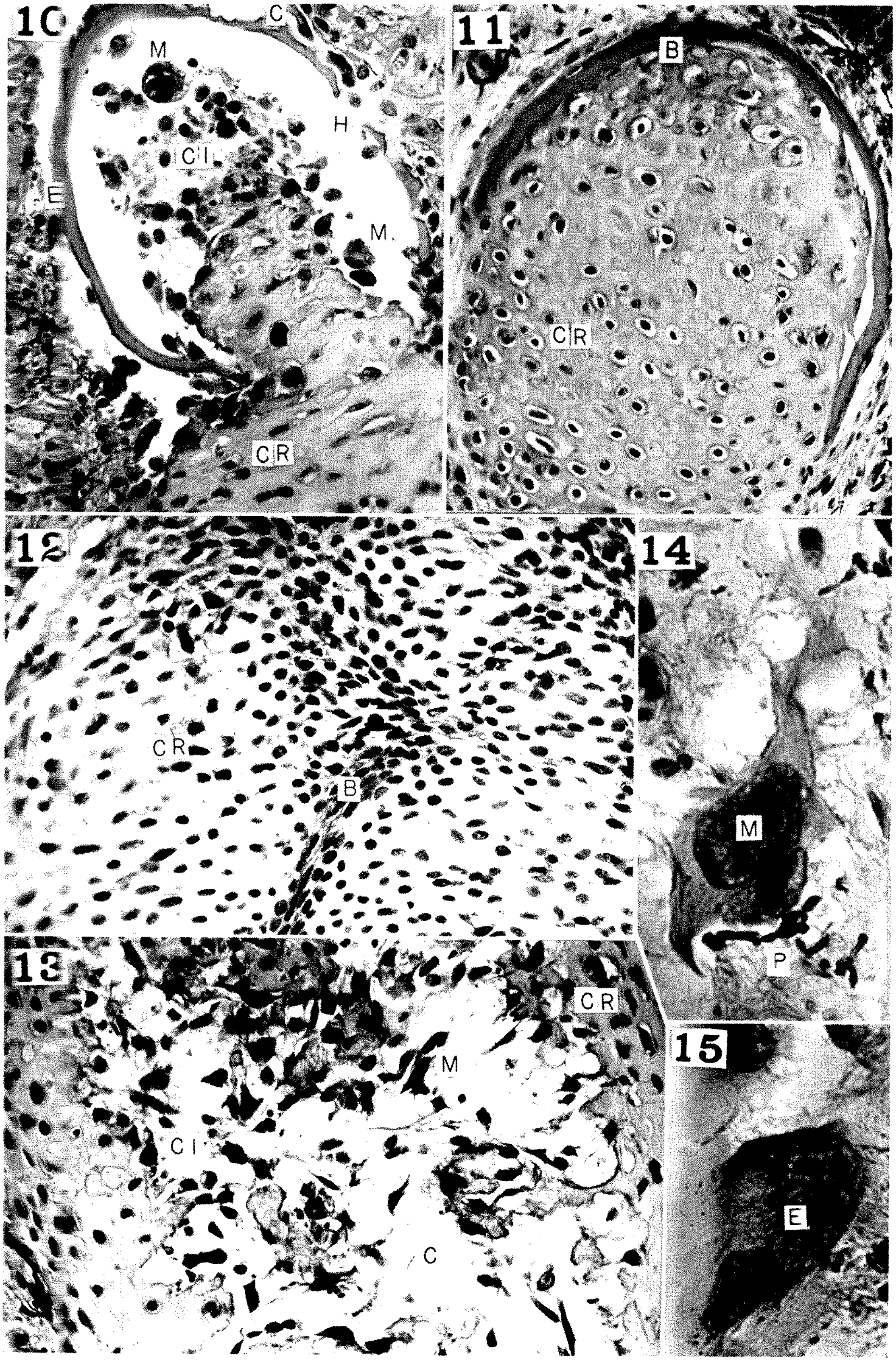
FIG. 11. Limb regenerate of a control animal. B—normal exterior bone layer; CR—normal cartilage. Photomicrograph ×150.

FIG. 12. Limb regenerate of axolotl (No. 13) 126 days after local irradiation with 4,000 r, showing distal portion of skeleton which appears normal. B—border between skeletal elements; CR—cartilage. Photomicrograph ×150.

FIG. 13. Limb regenerate of the same axolotl (No. 13) shown in Figure 12. This shows a more proximal portion of skeleton, which is greatly damaged. C—cavities in cartilage; CI—isolated cartilaginous cells; CR—cartilage which appears normal; M—macrophages. Photomicrograph ×100.

FIG. 14. Limb regenerate of axolotl (No. 13) 126 days after local irradiation with 4,000 r. M—giant macrophage in loose connective tissue; P—pigment cell. Photomicrograph ×500.

FIG. 15. Limb regenerate of axolotl (No. 17) 63 days after local irradiation with 4,000 r. E—giant epithelial cell from the lower layer of epithelium, resembling a giant macrophage. Photomicrograph ×500.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phagocytized connective tissue or cartilaginous cells, were found in these giant cells.

BLOOD VESSELS

Blood vessel damage was observed in 70–75 per cent of the animals that were irradiated with 4,000 r and in all animals irradiated with 6,000 r.

Early damage consisted of an increased number of small capillaries and vessels and an abnormal dilatation of the vessels. Advanced damage was characterized by the disappearance of the blood vessel walls with the formation of large sinuses, often immediately under skin epithelium.

Figure 29 shows a normal blood vessel; the endothelial cells are clearly seen. During the process of reduction, the distal portions of blood vessels gradually disappeared and, therefore, large blood vessels near the distal end of the limb were transformed into sinuses (Fig. 26). Many blood cells were observed in the connective tissue and an abnormally great accumulation of these cells was often seen in sinuses between the cartilaginous skeleton and epithelium (Fig. 27). The complete absence of endothelial cells was evident under higher magnification, in great contrast to the appearance of normal blood vessels (Fig. 28 and 29).

LOOSE CONNECTIVE TISSUE AND MUSCLES

Macrophages of various sizes were almost always found in the loose connective tissue, which has an important role in their distribution and spread. Through the connective tissue they can penetrate into the bone, cartilage, muscles, and other tissues and structures.

Some macrophages in loose connective tissue were small, being only twice as large as the connective tissue cells (Fig. 37). Others were three times as large as the connective tissue cells (Fig. 30, 31, 32 and 33), and in some places were accumulated in great numbers (Fig. 32). The largest macrophages, four to six times larger than connective tissue cells (Fig. 14 and 38), were found comparatively rarely and usually one or two such cells were isolated from the other macrophages.

During reduction, the amount of loose connective tissue and the number of connective tissue cells decreased greatly and was probably related to the activity of macrophages.

In some cases giant fibroblasts were noted (Fig. 44). Their appearance after total body irradiation with 6,000 r has already been described.[12] Apparently these cells were formed as a result of tissue reac-

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PLATE IV.

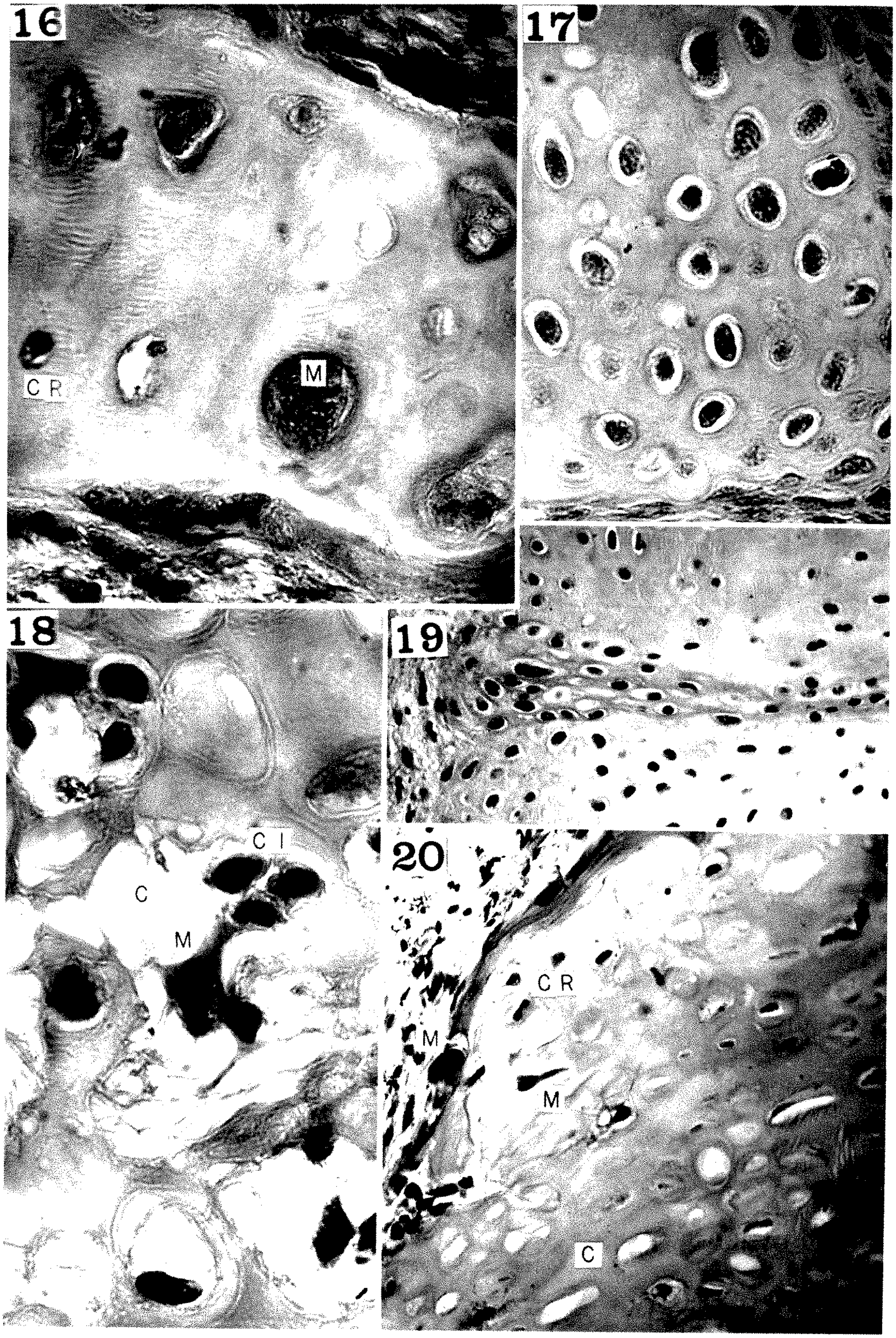
FIG. 16. Limb regenerate of axolotl (No. 21) 63 days after local irradiation with 4,000 r. CR—cartilage cell; M—inactive macrophage in the cartilage. Photomicrograph ×500.

FIG. 17. Limb regenerate of a control animal. Normal cartilage. Photomicrograph ×500.

FIG. 18. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. C—cavity in cartilage; CI—isolated cartilaginous cells; M—macrophages. Photomicrograph ×500.

FIG. 19. Limb regenerate of control animal. Normal cartilage. Photomicrograph ×150.

FIG. 20. Limb regenerate of axolotl (No. 7) 63 days after local irradiation with 4,000 r. C—cavity in cartilage; CR—cartilage cells; M—macrophage. Photomicrograph ×150.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tion to irradiation and were not related to the phenomenon of reduction.

Damage and disappearance of muscles were observed in 67 per cent of the animals fixed 63–65 days after irradiation with 4,000 r, and in all the animals irradiated with 6,000 r. In the process of reduction, compact muscle bundles (Fig. 34 and 41) were transformed into isolated small thin muscle bundles or even isolated muscle fibrils and separated nuclei. The appearance of muscle tissue undergoing reduction (Fig. 36) was in great contrast to normal muscle tissue (Fig. 34). Only separate, irregularly oriented, isolated muscle bundles and nuclei were seen. Between them macrophages were found. During more advanced reduction of this tissue (Fig. 35), only isolated muscle nuclei and remnants of muscle bundles, along with a great number of giant macrophages and many connective tissue cells, were found (Fig. 35 and 40). When muscle resorption was complete, the number of macrophages in that area also decreased.

The disappearance of muscles appeared to be related to the activity of macrophages and was probably the result of lytic enzymes secreted by these cells. Although actual phagocytosis was not observed, it is possible that muscle nuclei can be engulfed by macrophages. Inclusions found in the protoplasm of some macrophages appeared to be engulfed muscle nuclei (Fig. 40).

THE TEETH

The resorption of teeth of young axolotls irradiated with 2,000 r or 4,000 r 20 days after hatching and with 3,000 r 60 days after hatching has been described.[16] The teeth disappeared quickly. Forty-three days after irradiation, only small remnants of teeth were found, and within 10 days, even the remnants had completely disappeared. Some observations showed that macrophages play an active part in the destruction of the teeth in young animals.

The resorption of teeth of adult axolotls irradiated with 6,000 r has been described by us.[14] The teeth began to disappear about 50 days after irradiation and disappearance was usually complete within another 10 to 15 days. This process was the result of the activity of the macrophages. A new generation of teeth, much smaller and irregular in shape and position, then began to form. About 150 days after irradiation, almost all of these second generation teeth had disappeared, again as a result of the activity of the macrophages. Under the roots of some of the teeth, the macrophages were clearly seen (Fig. 42 and 43).

THE LENS

The resorption of lens 40–80 days after irradiation of the head of young axolotl with 3,000–6,000 r has also been described.[18] Serious damage was observed in 29 per cent of all irradiated animals. Dissolution of the lens fibers progressed gradu•

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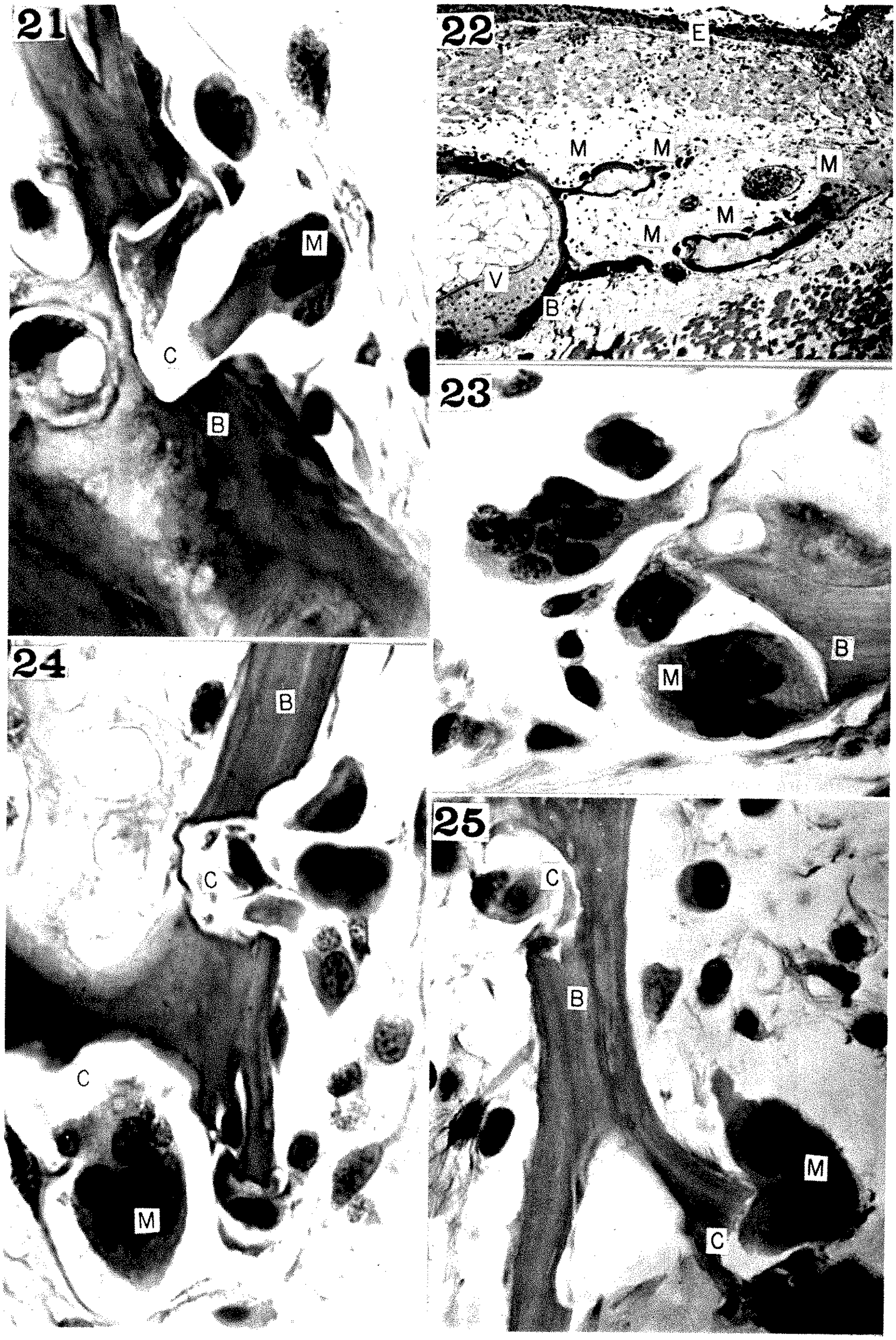
PLATE V.

FIG. 21–25. Portions of longitudinal sections through the tail of young axolotl (No. P-39) 209 days after local irradiation with 1,000 r. B—bone; C—cavity in the bone; E—skin epithelium; M—giant macrophages; V—vertebral body. Photomicrographs ×35 (FIG. 22), ×500 (FIG. 21, 23, 24, and 25).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ally and in most cases only remnants of the lens were found. The lens membrane, forming many small folds, was the most resistant structure. In some cases, macrophages were found in the body of the seriously damaged lens. Apparently, they partially phagocytized and partially dissolved the lens fibers, resulting in destruction of the lens.

DISCUSSION

The resorption process is the result of the reaction of the nonirradiated body to the irradiated limb. The most typical phenomenon in the tissue undergoing resorption is the presence of macrophages.

Resorption after roentgen irradiation is the result of the activity of the macrophages. The disappearance of the skeleton is the main factor in reduction; soft tissues without skeletal support contract and are destroyed more easily by macrophages. Blood vessel damage is probably also an important factor. During advanced reduction all distal capillaries and small blood vessels are destroyed. As a result, many of the large distal blood vessels are transformed into peripheral sinuses. Resorption apparently occurs in the presence of an abnormal blood supply, which may create conditions favorable for its advance. An abnormal blood supply favors the transportation of macrophages into the limb undergoing resorption and, through formation of large sinuses directly under the skin, favors the reduction of skin epithelium.

The resorption which results from macrophage activity may be the specific reaction of amphibians to local irradiation. Reduction or resorption is observed during normal development in certain amphibians. The resorption of tails at the time of metamorphosis of Anura tadpoles is a classic example of such reduction. But resorption in some degree is observed also in Urodella, *i.e.*, the disappearance of the gills and the transformation of the tail during metamorphosis, when the axolotl is transformed into the adult form, Amblystoma. Bataillon,[2] Duesberg,[20] Aleshin,[1] and others showed that resorption of the tadpole's tail occurs by means of phagocytosis and histolysis. Aleshin[1] found large aggregations of macrophages in the tail of the metamorphosing tadpole and showed that resorption of the tail begins and progresses the same as typical inflammation.

Butler[17,18] observed resorption of the cartilaginous skeleton of irradiated regen-

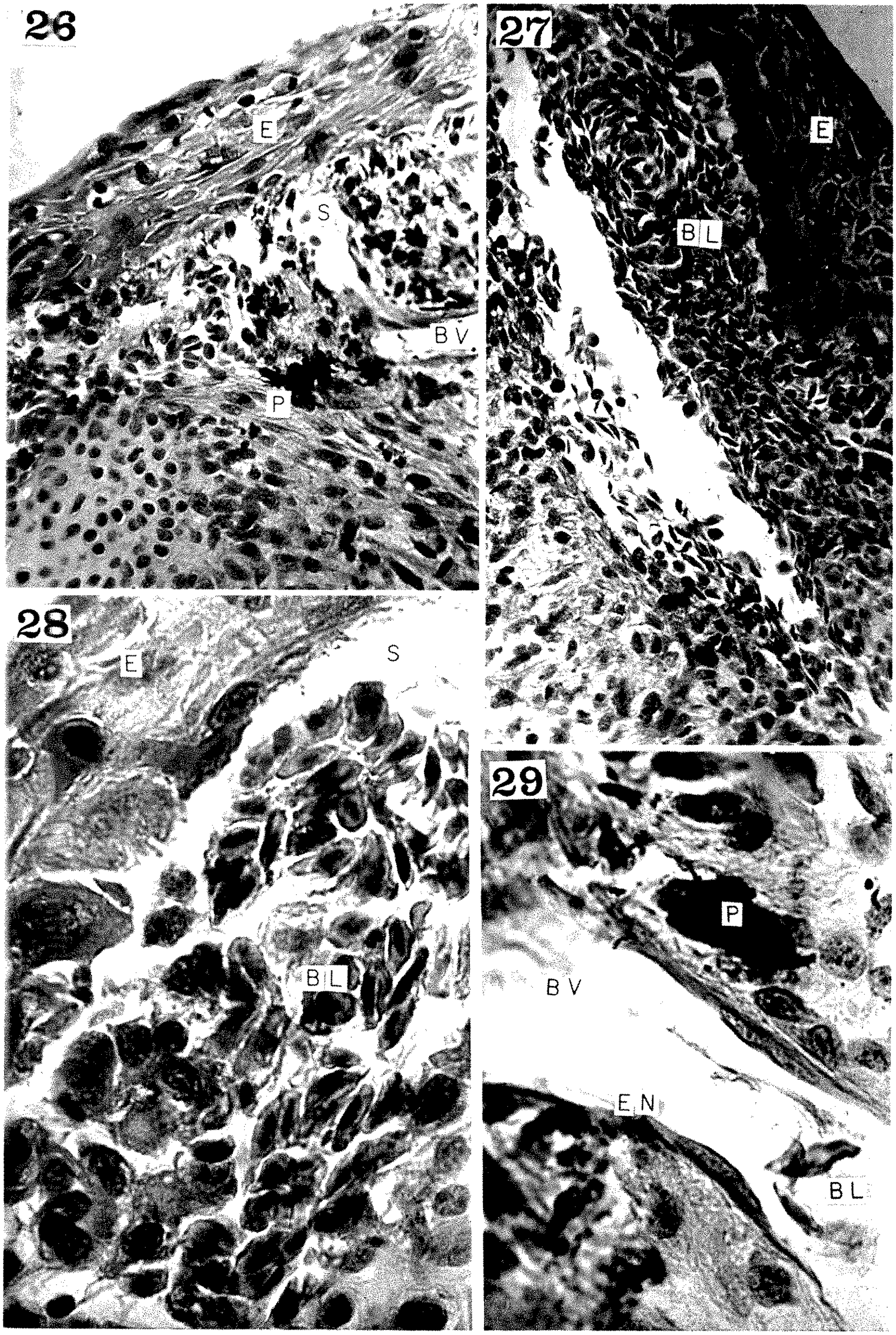
PLATE VI.

FIG. 26. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. BV—large blood vessel transformed into subepithelial sinus (S); E—skin epithelium; P—pigment cell. Photomicrograph ×150.

FIG. 27. Limb regenerate of axolotl (No. 20) 62 days after local irradiation with 4,000 r. BL—accumulation of blood corpuscles in sinus under skin epithelium (E). Blood vessel walls are absent. Photomicrograph ×150.

FIG. 28. The same specimen as that in Figure 27, under higher magnification. Photomicrograph ×500.

FIG. 29. The same specimen as that in Figures 27 and 28, showing normal endothelial cells (EN) of the blood vessel (BV) from a more proximal region of the limb. P—pigment cell. Photomicrograph ×500.


26
E
S
BV
P
27
E
BL
28
E
S
BL
29
P
BV
EN
BL

eration buds in larval stages of Amblystoma punctatum. This disintegration of the cartilaginous skeleton proceeds in a proximal direction. Puckett[21,22] also observed resorption of tissues after irradiation of Amblystoma larvae. Puckett described "giant" cells which were observed during resorption, but did not ascribe any particular significance to them. In spite of the fact that these authors give a completely different interpretation of their findings and suggest a hypothesis of excessive differentiation, they undoubtedly observed the same phenomenon of roentgen regression.

The process of reduction in amphibians is not caused by roentgen treatment alone. For example, regenerating limbs in triton are resorbed following destruction of their innervation.[3,22] Also, the denervated nonregenerating limbs of Amblystoma punctatum, Amblystoma opacum, and Triturus viridescens are resorbed.[18,23]

We conclude that regression or resorption is the specific reaction of amphibians to roentgen radiation or certain other factors and is related to the ability of these animals to undergo transformation during metamorphosis.

SUMMARY

1. Reduction was observed in 90 per cent of the regenerated limbs of adult axolotls irradiated with 4,000 r, and in 100 per cent of those irradiated with 6,000 r. Reduction begins in the distal end and progresses proximally. The skin epithelium is gradually reduced in area without the formation of open wounds.

2. Histologic investigation showed that the conditions of the skin epithelium depended upon the interval between irradiation and fixation. In most cases, early fixation (40–80 days after irradiation) revealed epithelial damage, *i.e.*, formation of giant cell degenerating epithelium, while late fixation (100–128 days after irradiation) revealed normal epithelium. The condition of the epithelium is the result of a specific reaction of this tissue and is independent of the reduction of the limb in general. The mechanism of the epithelium reduction is obscure, but it is independent of macrophage activity. A hypothetical explanation is given. Damage of the subcutaneous pigment layer or separate pigment cells was observed in all cases, but the condition of these cells varied greatly in different areas of the limb.

→

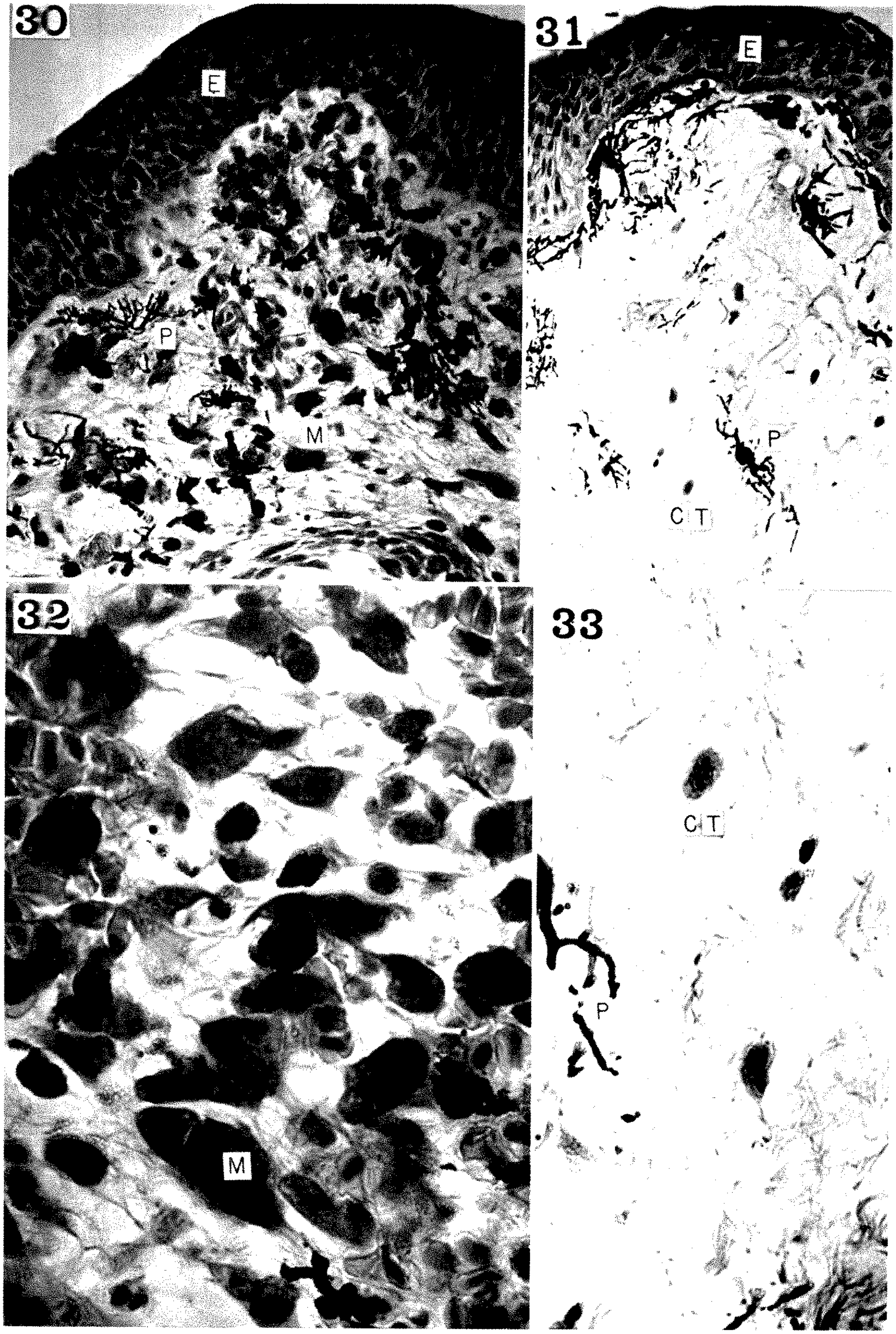
PLATE VII.

FIG. 30. Limb regenerate of axolotl (No. 16) 126 days after local irradiation with 4,000 r. E—skin epithelium, normal in appearance; M—macrophages in loose connective tissue; P—pigment cell. Photomicrograph ×150.

FIG. 31. Limb regenerate of the same animal as that in Figure 30, showing a more proximal, probably nonirradiated, region. CT—cells of loose connective tissue; E—epithelium, normal in appearance; P—pigment cell. Photomicrograph ×50.

FIG. 32. Part of the section through the limb regenerate of axolotl (No. 15) 63 days after local irradiation with 4,000 r, showing an accumulation of macrophages (M) in loose connective tissue. Photomicrograph ×500.

FIG. 33. Limb regenerate of the same animal as that in Figure 31. CT—cells of loose connective tissue; P—pigment cell. Photomicrograph ×500.


30
E
P
M
31
E
P
C T
32
M
33
C T
P

3. Resorption of the cartilaginous and bony skeleton is a result of macrophage activity. The attack of macrophages on the skeletal elements always begins at the surface. Bone and cartilage are dissolved as a result of the action of lytic enzymes secreted by macrophages which are located near the skeletal surface. Comparatively small macrophages penetrate deeply into the cartilaginous substance and dissolve the cartilage, forming many empty spaces in various areas. Such spaces are never observed in normal cartilage.

4. During advanced reduction all distal capillaries and small blood vessels disappear and in many cases the large blood vessels in the distal regions are transformed into peripheral sinuses. Resorption occurs in the presence of abnormal blood supply.

5. The loose connective tissue has an important role in the distribution and spread of macrophages. Through this tissue the macrophages can penetrate into the bone, cartilage, and other tissues. During the resorption, the amount of connective tissue is decreased greatly, probably as a result of macrophage activity.

6. During reduction, compact muscle bundles are reduced to isolated small, thin bundles or even isolated, irregularly oriented fibrils and isolated nuclei. Macrophages are found between them. Resorption of muscles is a result of macrophage activity.

7. Resorption of teeth of young and adult axolotls, once it has begun, is completed quickly within 10–15 days and is the result of macrophage activity.

8. Resorption of the lens of the young axolotl after irradiation of the head is the result of macrophage activity.

9. Regression, reduction, or resorption is the result of reaction of the nonirradiated body to the irradiated portion, and is the direct result of macrophage activity.

10. Resorption is a specific reaction of amphibians and is observed during normal development at the time of metamorphosis.

11. Resorption can be provoked by roentgen rays or other factors. This re-

PLATE VIII.

FIG. 34. Limb regenerate of a control animal, showing normal muscle tissue. N—nuclei. Photomicrograph ×150.

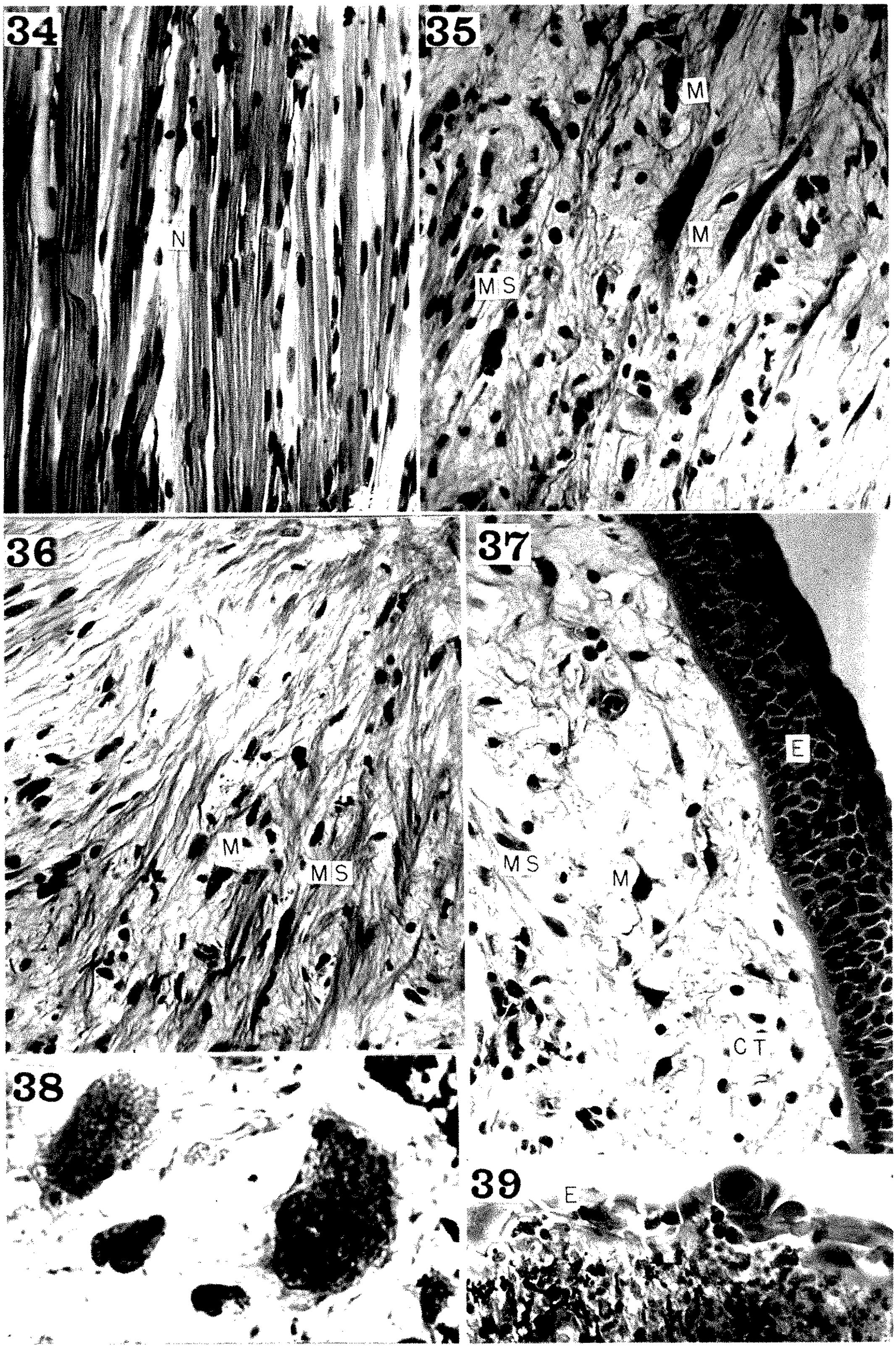
FIG. 35. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r, showing reduction of muscle tissue. M—giant macrophages; MS—muscle nuclei. Photomicrograph ×150.

FIG. 36. Part of the section through the limb regenerate of axolotl (No. 13) 126 days after local irradiation with 4,000 r, showing early stage of muscle reduction. M—macrophages; MS—muscle nuclei. Photomicrograph ×150.

FIG. 37. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. CT—connective tissue cells; E—skin epithelium; M—macrophage; MS—muscle nuclei. Photomicrograph ×150.

FIG. 38. Limb regenerate of axolotl (No. 13) 126 days after irradiation with 4,000 r, showing giant macrophages. Photomicrograph ×500.

FIG. 39. Limb regenerate of axolotl (No. 17) 63 days after irradiation with 4,000 r. E—giant cell abnormal skin epithelium, consisting of one layer of cells. Photomicrograph ×150.


34
N
35
M
M
MS
36
M
MS
37
E
MS
M
CT
38
39
E

sponse is related to the ability of these animals to undergo transformation during metamorphosis.

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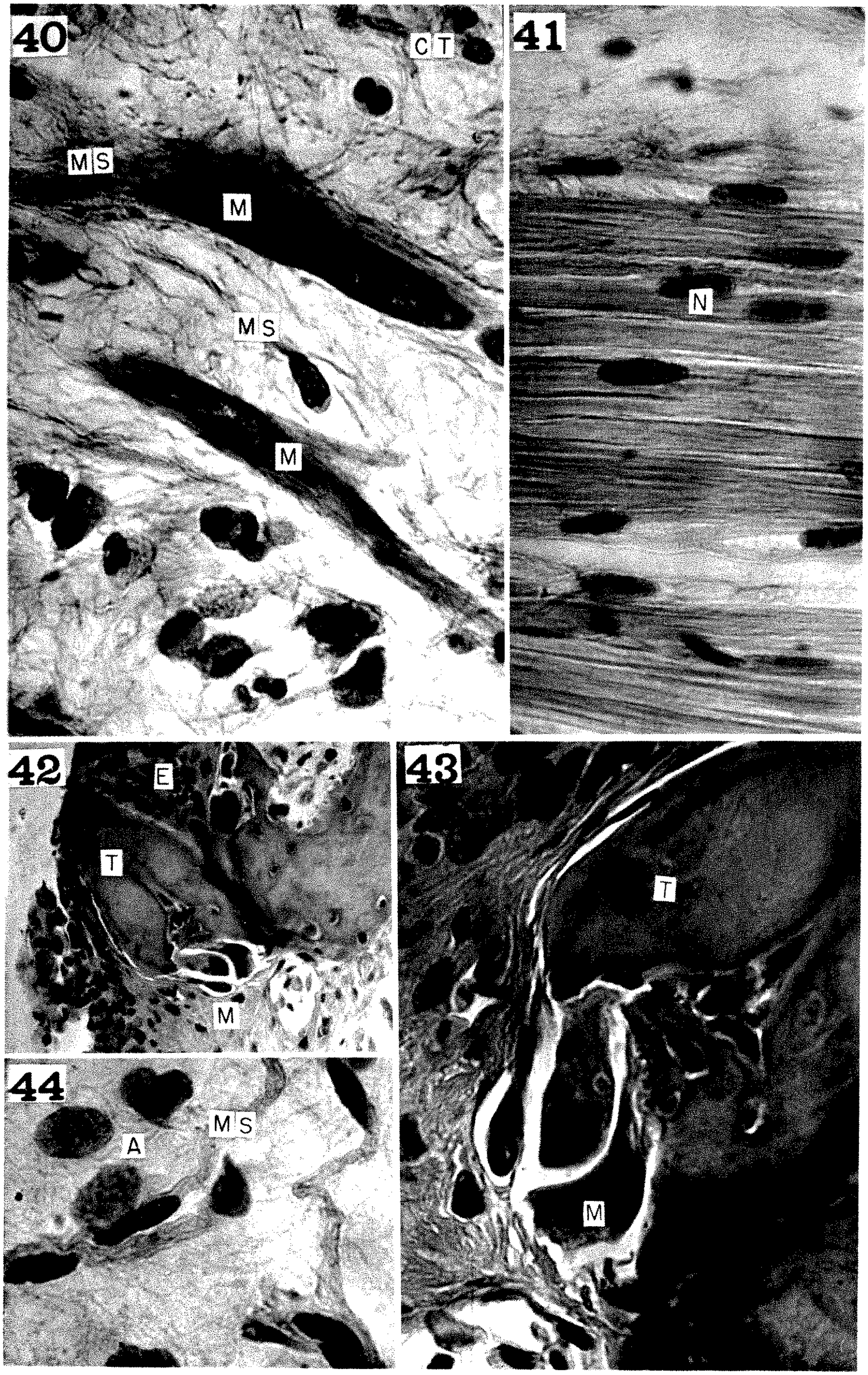
PLATE IX.

FIG. 40. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. CT—connective tissue cells; M—giant macrophages; MS—remnants of muscle fibers. Photomicrograph ×500.
FIG. 41. Limb regenerate of control animal. Normal muscle tissue. N—nuclei. Photomicrograph ×500.
FIG. 42. Sagittal section through the jaw of an adult axolotl (No. 17) 144 days after irradiation with 6,000 r. E—oral epithelium; M—macrophages; T—tooth. Photomicrograph ×150. (Reproduced with permission from the *Journal of Dental Research*, 1959, *38*, 301.)
FIG. 43. The same section as that in Figure 42 under higher magnification. Photomicrograph ×500. (Reproduced with permission from the *Journal of Dental Research*, 1959, *38*, 301.)
FIG. 44. Limb regenerate of axolotl (No. 17) 63 days after irradiation with 4,000 r. A—abnormal connective tissue cells; MS—muscle fiber. Photomicrograph ×500.


40
CT
MS
M
MS
M
41
N
42
E
T
M
43
T
M
44
MS
A

upon teeth of adult axolotl (Siredon mexicanum). *J. Dent. Research*, 1959, *38*, 301–310.

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THE RESPONSE OF SWINE AFTER EXPOSURE TO THE GAMMA-NEUTRON FLUX OF A NUCLEAR DETONATION*

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ALTHOUGH the responses of large mammals exposed to acute whole-body gamma irradiation from a nuclear detonation,[1,13,14] from cobalt 60 gamma rays,[6,10] 1 mv. peak[16] and 2 mv. peak[12] roentgen rays have been well documented, the effects of mixed gamma and neutron radiations from a nuclear detonation have not been reported. Swine, which have a cross sectional diameter similar to that of man, are of particular interest as experimental animals since comparable distributions of depth doses are obtained. The present study was performed during the summer of 1957 (Operation Plumbbob) at the Nevada Test Site to evaluate the responses of swine after exposure to a wide range of prompt radiation doses from a nuclear detonation with a gamma-neutron dose ratio of 1.2. The range of exposure doses obtained was from 410 to 2,475 rads, which afforded a unique opportunity to compare various levels of effect on a population of large mammals. Parameters investigated were physical signs of illness, acute lethality through 45 days, and median survival times.

METHODS

The swine were a Hampshire-Landrace strain with occasional swine having Duroc coloration. They were obtained from a midwest breeder and shipped by double-decked truck to the exposure site. The animals were free from disease and external parasites and were immunized against hog cholera and swine erysipelas. The animals were fed a 14 per cent protein ration and had not received antibiotics in their feed except at weaning (third week). Water was available ad libitum.

Two hundred and sixty-four animals (47 per cent male castrates—53 per cent females) were selected for uniformity of weight (83 ± 11 pounds) and assigned to exposure groups by a system of random numbers.

The animals were exposed in aluminum cylinders (wall thickness $\frac{1}{4}$ inch) anchored to the ground by cables and stout metal pegs (Fig. 1). Two pigs were placed in each cylinder and 12 animals were exposed at each dose level. After exposure the animals were checked for external radioactive contamination and placed in pens, 24 per pen. Observations were made at frequent intervals thereafter.

Neutron measurements were made in air using threshold detectors of activation foils and fission foils.[3] The foils used and the neutron energy ranges measured directly by activation or by the difference between fission thresholds were:

Foil	*Neutron Energy Range*
Sulfur	Greater than 2.5 mev.
Uranium minus sulfur	1.5 mev. to 2.5 mev.
Neptunium minus uranium	750 kev. to 1.5 mev.
Plutonium minus neptunium	4 kev. to 750 kev.

Neutron fluxes at all energy bands measured decreased exponentially with distance from the detonation; however, the proportion of neutrons in the various energy

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Fig. 1. Aluminum exposure cylinders for swine anchored in place in exposure area.

ranges was unchanged over the distances at which swine were exposed. From the neutron flux measurements, neutron doses were obtained in rads from single collision theory using the following conversion values[4] for each neutron energy range of exposure:

Neutron Energy	*Flux per 1 rad*
Greater than 2.5 mev.	2.5×10^8 n/cm^2
1.5 mev. to 2.5 mev.	3.2×10^8 n/cm^2.
750 kev. to 1.5 mev.	4×10^8 n/cm^2.
4 kev. to 750 kev.	1×10^9 n/cm^2.

The gamma-neutron dose ratio changed by about eight per cent over the range of animal exposures due to the shorter mean free path of neutrons as compared to gamma rays. The average neutron contribution to the total (gamma plus neutron) rad dose delivered was:

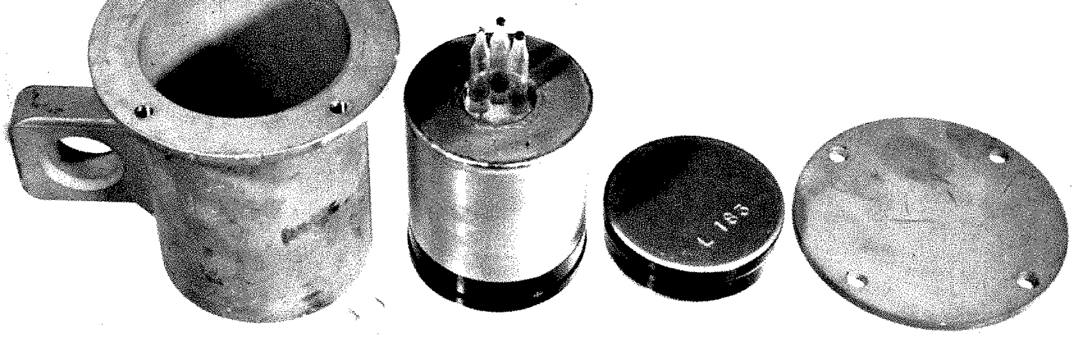
Neutron Energy	*Per Cent Neutron Contribution to Total Exposure Dose*
Greater than 2.5 mev.	10
1.5 mev. to 2.5 mev.	8
750 kev. to 1.5 mev.	13
4 kev. to 750 kev.	14

Gamma ray and neutron measurements were made in air using chlorinated hydrocarbon dosimeter systems. The characteristics of the gamma sensitive (hexylresorcinol stabilized, tetrachloroethylene) and gamma plus neutron sensitive (trichloroethylene overlayed with a water soluble indicator) chemical dosimeters have been reported in detail.[8,9] The dosimeter vials were contained in lithium lined aluminum cans (Fig. 2) to eliminate thermal neutron response of the system. Acidimetric color changes were determined spectrophotometrically and gamma and neutron doses are expressed in rads.

RESULTS

RADIATION RESPONSES IN SWINE

At the time of recovery (about one hour) one animal (1,160 rad group) was found dead as a result of a fractured cervical vertebra. The remaining animals appeared in good condition and there was no evidence that vomiting had occurred in any group. A few swine vomited shortly thereafter during the return trip to the pen area. On arrival at the pen area all swine appeared to eat and drink normally.



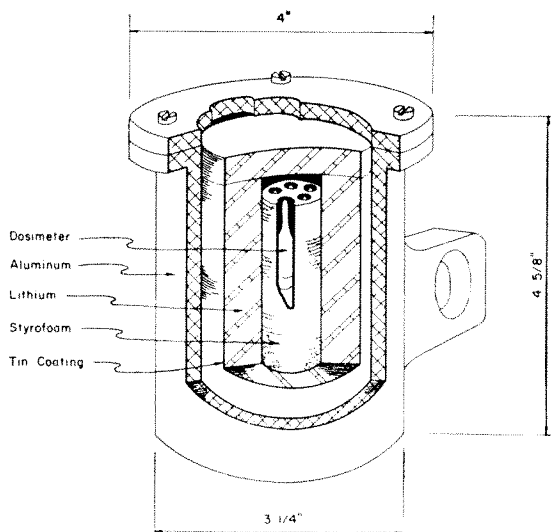


FIG. 2. Schematic drawing and components of chemical dosimeter with aluminum protective can, lithium insert, and glass vials containing organic chemical detector.

The manifestations of acute radiation disease in swine showed three rather distinct phases after gamma-neutron exposure. In general, as the dose was increased, the onset of each phase was more rapid and signs more pronounced.

1. Responses Associated with Exposures from 1,730 to 2,475 rads. Late on the first day after irradiation the swine showed a moderate reduction in volitional activity. At the twenty-four hour feeding there was little food intake and by thirty-six hours intake was nil. All animals in this dose range were vomiting within forty-eight hours and the frequency and severity increased with time. Extreme polydipsia followed by copious vomiting was common. The onset of diarrhea also occurred about forty-eight hours after exposure and consistency rapidly changed from soft stools to a copious watery discharge. Although polydipsia and vomiting subsided late in the third day, diarrhea persisted in most swine until death. Irritability and hyperesthesia were evident late in the second day and most pronounced on the third day. After irritability and hyperesthesia subsided late in the third day the swine were listless and severely ill. Rectal temperatures in some swine rose to 106–109°F. In keep-

ing with the gaunt appearance of the animals was the measured decrease in body weight.

The mode of death varied in this range of exposure doses. Many swine died quietly in deep coma, whereas others had repeated episodes of convulsive activity for several hours prior to death. Death occurred in 106–112 hours. This was similar to the stable 3.5 to 4 day or "gastrointestinal" death seen in rodents after roentgen- and gamma-ray exposures from 1,200 to 10,000 r.

2. Responses Associated with Exposures from 575 to 1,535 rads. Anorexia and vomiting occurred later than for the previous group and their incidence, severity and duration were not marked in the early stages. Vomiting became severe later at the higher doses, with some swine vomiting gross blood. Most of these swine had a transient return of appetite between the fifth and seventh days post irradiation, yet became gaunt and emaciated with a rough hair coat prior to death.

The onset of diarrhea occurred on the fourth and fifth days post exposure. In many swine bloody stools were noted by the end of the first week. Blood clots and gross blood were passed with considerable straining in some animals, while others bled freely while lying down.

By the seventh day bloody froth and bright red blood exuded from the nostrils in many swine. The onset of cutaneous petechiae and/or purpura was noted from the eighth to the twelfth day, appearing on the ventral surface of the abdomen or the medial surfaces of the appendages. These areas developed a livid appearance as the hemorrhagic lesions coalesced. A similar lividity was seen in the ears in the terminal stages of the illness. Frequently swine in this group survived three or four days after the onset of bleeding. Edema of the appendages and rarely of the snout, not seen at higher doses, appeared from the seventh to the twelfth day.

Gross and ophthalmoscopic observations revealed only extreme congestion of the sclerae throughout the illness.

3. Responses Associated with Exposures from 410 to 515 rads. The syndrome associated with median lethal doses was characterized by a transient loss of appetite and vomiting and diarrhea which occurred about the third day. This was followed by a period of apparent normal health and continued weight gain until the appearance of the hemorrhagic syndrome at 8 to 10 days following exposure. Hemorrhagic signs were more pronounced in those animals which eventually succumbed, yet which lived sufficiently long for manifestations of granulocytopenia and thrombocytopenia to develop fully. Bleeding from body orifices, elevated temperature, and ataxia were significantly more frequent in decedents. Death usually occurred on the fourteenth or fifteenth day and this phase of radiation sickness has been described in detail for a variety of experimental animals.

LETHALITY

Listed in Table I are the percentages of deaths at 30 days for swine exposed to graded doses of gamma rays and neutrons. When per cent mortality was plotted against dose, a sigmoid response curve was obtained. Probit transformation of the data using the method described by Finney[2] gave a regression line of the type.

$$Y = a + bx$$

where Y was the probit of per cent mortality and x was log radiation dose in rads. Figure 3 shows the relationship of per cent mortality for varying doses of gamma plus neutron irradiation. Median lethal doses at various times after exposure are listed in Table II. The LD_{50} at 45 days was not altered from the 30 day value by the death of the one animal at the forty-second day post exposure.

MEDIAN SURVIVAL TIME

Median survival time at each dose level was determined by plotting probit of per cent survival against the logarithm of time from exposure. The best line of fit was

Table I

MORTALITY AND SURVIVAL TIMES OF SWINE AFTER GAMMA-NEUTRON IRRADIATION

Exposure Dose (rads)	Days after Irradiation																			Lethality (per cent)	Median Survival Time (hr.)
	1	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	42		
2,475		1	10	1																100	106
2,185		1	11																	100	107
1,935		2	6	4																100	112
1,730		3	6	3																100	109
1,535			3	7	1	1														100	125
1,325			2	7	3															100	134
1,300			3	5	2	1		1												100	137
1,205		1	1	5	1	3	1													100	139
1,160	1*			6	3	2														100	143
1,070			1	3	2	3	3													100	156
1,030			2	2	4	2	2													100	147
955				1	2	2	1	1	2	2				1						100	210
915					5	2	4			1										100	180
845					3	5	3		1											100	178
820					2	5	2	2											1	100	182†
760				1	2	3	1			2						1				83.3	182
730					1	2	1	5	1			2								100	218
645								1	2	4	3		1	1						100	273
575						1	1		3	2			1	1		1				83.3	270
515									1		1		2	1		1		1		58.3	350
455											1			1		1	1			33.3	360
410													1	1						16.7	360

* Animal dead on recovery, not included in lethality or survival time results.
† Not including animal dying on forty-second day.

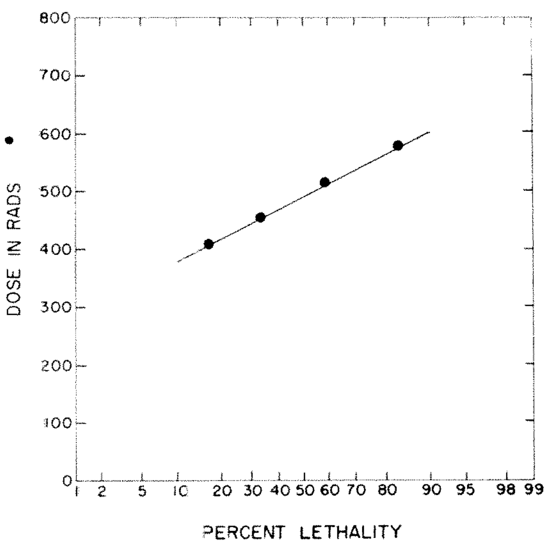


Fig. 3. Thirty-day lethality in swine as a function of dose of gamma-neutron irradiation from a nuclear detonation.

drawn through the data, and the point corresponding to a probit 5 or 50 per cent survival was taken as the median survival time. Survival times are listed in Table 1.

DISCUSSION

The physical signs of acute sickness in swine exposed to a wide range of gamma-

Table II

MEDIAN LETHAL DOSE AT VARIOUS TIMES AFTER EXPOSURE

Time after Exposure (da.)	Median Lethal Dose (rads)
5	1,570 (1,439–1,714)
10	711 (662– 764)
15	565 (514– 621)
30–45	486 (478– 496)

neutron doses from a nuclear detonation have been described. Although fission neutrons contributed about 45 per cent of the total dose delivered, there was little difference in the incidence, severity, and duration of acute radiation sickness in swine as compared to roentgen or gamma irradiation.[1,10,11,13,14,15]

Podalgia and abnormal gait were observed as reported in swine after cobalt 60 irradiation[10] and may be associated with hemorrhage into joint spaces as observed in this study and as reported elsewhere.[14] Ocular lesions reported after low dose rate exposures to cobalt 60 gamma rays[10] were not observed however.

The LD_{50} value of 486 rads at 30 days is in good agreement with values reported for swine and other large mammals after roentgen or gamma irradiation.[6,12,13,16] Considering the variations in biologic response and differences in exposure factors reflected in the $LD_{50/30}$ values obtained, the differences were, indeed, not large. The previously reported value of 230 r for swine exposed to gamma rays from a nuclear device[13] was significantly lower. In the present study neither gamma rays nor fission neutrons were obtained as discrete radiations. However, if an effectiveness of 1 is assigned to gamma rays and if the effect of gamma plus neutron irradiation is assumed to be additive, the relative effectiveness of fission neutrons is then about 1.2 (the gamma-neutron dose ratio) for the production of lethality.

The survival times of swine were similar to those seen in rodents and monkeys over the same range of doses; however, quantitative differences appeared to exist between swine and the other species. The median survival time for swine irradiated with doses of about the median lethal range was 14–15 days as compared to the 10–11 day death time of rodents. The dose dependent region of survival response occurred in swine after doses from 575 to 1,535 rads. A stable plateau in survival time of 4–5 days appeared to have been reached for the swine at somewhat higher total doses than for the 3½ day gastrointestinal death in rodents and monkeys. Since no group of swine had a median survival time less than 4–5 days, the threshold for "central nervous system death" was not exceeded and has been reported in excess of 2,475 rads.[7]

SUMMARY

1. The responsiveness of 264 swine exposed to doses from 410 to 2,475 rads of gamma-neutron radiation from a nuclear dentonation has been described.

2. The LD_{50} value at 30 days was 486 (478–496) rads.

3. Median survival times for swine were similar to those of other mammalian species.

4. The potency of fission neutrons as compared to gamma rays from a nuclear detonation was estimated to be about 1.2 for the production of lethality at 30 days in swine.

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Walter Reed Army Institute of Research
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The success of a radiation effects study of this nature, conducted under field conditions, is obviously contingent upon a variety of circumstances such as weather, source strength, and the close cooperation of a rather heterogenous group of scientific personnel. In large part these results are the efforts of the splendid group of noncommissioned officers and enlisted personnel assigned to the project.

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EDITORIAL

MULTIPLE MYELOMA AND INTRAVENOUS PYELOGRAPHY

IN 1933, Bell[1] advanced the theory that the excretion of Bence Jones proteins in the urine of patients afflicted with multiple myeloma leads to laminated deposits of hyaline casts in the renal tubules, exerting gradual mechanical obstruction followed by glomerular atrophy and chronic progressive uremia. Oliver[2] in 1945, through a series of morphologic demonstrations, supported this "stopped pipes" theory and he has shown that the deposition of laminated Bence Jones protein casts may occur in the entire nephron up to the proximal convoluted tubules. This concentric laminated appearance of the casts, together with the sequential changes resulting from the gradual obstruction produced by them, is so characteristic that at autopsy it often permits the establishment of a diagnosis of multiple myeloma from a study of the kidney alone. Consequently, the term of "myeloma kidney" was coined to express this pathognomonic significance. It must be mentioned, however, that paramyloidosis, secondary hypogammaglobulinemia and some alternative modes of Bence Jones protein damage may also play a role in producing the renal insufficiency. The presence of some kidney changes has been observed in 48–90 per cent of multiple myeloma patients in several series reported and uremia was found to be, after pneumonia, the most frequent cause of death.

Very recently Sanchez and Domz[3] gave an excellent account of the clinical manifestations which may be attributed to these kidney changes. They categorized the renal syndromes associated with multiple myeloma into: acute glomerulonephritis, nephrotic syndrome, water-losing nephritis, adult Fanconi's syndrome, renal tubular acidosis, acute tubular necrosis, and acute and chronic pyelonephritis. The most important observation made by Sanchez and Domz, however, is the fact that "renal disease is a common guise under which myeloma may masquerade and elude diagnosis" before other more tangible signs become apparent. This elusiveness was also noted by Osserman,[4] who in 2 cases fortuitously discovered dysproteinemia during the course of study for unrelated conditions and was able to establish the diagnosis of multiple myeloma before skeletal changes could be demonstrated roentgenographically. In one patient, who died with signs of hypercalcemia and renal functional impairment, both the documented asymptomatic and symptomatic periods were extremely brief. In the second patient skeletal changes developed one year after the discovery of the abnormal protein. The difficulty of diagnosis in occult multiple myeloma is further complicated by the additional facts that (a) at times extramedullary involvement of organs other than the kidney, as for example of the lung, pleura, retroperitoneal lymph nodes or testicle, may constitute the principal feature of the disease and (b) a 5 per cent incidence of the Bence Jones proteinuria or dysproteinemia is observed in such conditions as malignant lymphomas, metastatic tumors of bone, idiopathic hemolytic disease, the "essen-

[1] BELL, E. T. Renal lesions associated with multiple myeloma. *Am. J. Path.*, 1933, *9*, 393–420.

[2] OLIVER, J. New directions in renal morphology: method. Its results and its future. Harvey Lecture (1944–1945), 1945, *40*, 102–155.

[3] SANCHEZ, L. M., and DOMZ, C. A. Renal patterns in myeloma. *Ann. Int. Med.*, 1960, *52*, 44–54.

[4] OSSERMAN, E. F. Natural history of multiple myeloma before radiological evidence of disease. *Radiology*, 1948, *71*, 157–174.

tial" cryoglobulinemia and very rarely in a few other lesions.

The proper evaluation of myeloma kidney and associated or related lesions is of considerable interest to the radiologist since recent evidence is accumulating which shows that it is hazardous to perform intravenous pyelography in patients afflicted with such lesions. In cases with frank multiple myeloma, precise assay of the renal involvement is usually not difficult and the danger thus can easily be avoided. However, in the occult cases and especially in those in which the renal disease is not even suspected as reflecting the main clinical feature of a possible myelomatous process, the use of intravenous pyelography may prove disastrous.

Bartels, Brun, Gammeltoft and Gjørup[5] were the first to make this observation in 1954. They performed intravenous pyelography in a male, aged sixty-nine, who complained of fatigue and flank pain; he had increased blood urea nitrogen and proteinuria, but no Bence Jones protein. The patient, who was suspected of having myelomatosis, developed "acute" anuria following the intravenous pyelography and died forty days later. At postmortem examination casts were found extensively filling the tubules. In 1956, Myhre, Brodwall and Knutsen[6] reported 2 similar cases. One patient, a male aged seventy, died eleven days after intravenous pyelography. The other, a male aged forty-two, recovered from the acute episode but died in uremia eight months later. At postmortem examination cast-plugged tubules were the outstanding finding. In 1957, Kielmann, Gjørup and Thaysen[7] reported the case of a male, aged thirty-six, with multiple myeloma, who had marked proteinuria with demonstration of abnormal proteins. This patient went into acute renal failure immediately after the intravenous pyelography and died nine days later. At postmortem examination only a few casts were found in the tubules.

In 1958, Perillie and Conn[8] analyzed in detail the various aspects of the above mentioned cases and reported an additional case of their own. In this case, a male thirty-four years old, proteinuria and hyperglobulinemia were present and roentgenograms revealed general osteoporosis with small multiple osteolytic lesions of the vertebral bodies and ribs. Plasma cell myeloma was suspected. Intravenous pyelography was performed which showed normal excretion of the contrast medium and normal structures. Nausea and vomiting developed on the day after pyelography and the subsequent course was one of progressive renal failure complicated by recurrent epistaxes, nausea, and vomiting. He died in uremia almost three months after pyelography. Postmortem examination revealed that the tubules which were markedly dilated were filled, particularly in the proximal portions, with inspissated casts in varying stages of formation. Perillie and Conn also mention another case of plasma cell myeloma, personally communicated to them by Walsh, in which anuria was induced by intravenous pyelography resulting in the death of the patient.

Sanchez and Domz[3] report a case of occult multiple myeloma in which the dominant clinical picture was hypertensive azotemia and intravenous pyelography was performed in the hope of uncovering a correctable renal lesion. The patient died with congestive heart failure and postmortem examination disclosed multiple myeloma, with generalized arteriolar paramyloidosis, particularly severe in the kidney. It is the opinion of Sanchez and Domz that hypertensive, instead of the usual normotensive, azotemia may occur in multiple myeloma in

[5] BARTELS, E. D., BRUN, G. C., GAMMELTOFT, A., and GJØRUP, P. A. Acute anuria following intravenous pyelography in patient with myelomatosis. *Acta med. scandinav.*, 1954, *150*, 297–302.

[6] MYHRE, J. R., BRODWALL, E. K., and KNUTSEN, S. B. Acute renal failure following intravenous pyelography in cases of myelomatosis. *Acta med. scandinav.*, 1956, *156*, 263–266.

[7] KIELMANN, S., GJØRUP, S., and THAYSEN, J. H. Fatal acute renal failure following intravenous pyelography in patient with multiple myeloma. *Acta med. scandinav.*, 1957, *158*, 43–46.

[8] PERILLIE, P. E., and CONN, H. O. Acute renal failure after intravenous pyelography in plasma cell myeloma. *J.A.M.A.*, 1958, *167*, 2186–2189.

the presence of paramyloidosis or as a result of renal ischemia and may completely overshadow the basic disease, as in their own case. They also state that in retrospect the attempt at intravenous pyelography appears to have been unwise. They believe that multiple myeloma may be present sometimes for years in an occult form, detectable only when searched for, and that if such patients have renal involvement disaster may be precipitated with "disconcerting swiftness" after minor stress.

The well known survey of 1955 by Pendergrass, Hodes, Tondreau, Powell and Burdick[9] on the deaths and unfavorable sequelae following the administration of contrast media in urography encompasses more than 3,800,000 urographic examinations over an eleven year period. There were 25 immediate deaths which were attributed to allergic reactions. In addition, there were 3 delayed deaths which occurred one, two and three days, respectively, following intravenous pyelography. All 3 of these patients had increased blood urea nitrogen and died in uremia. Since the clinical findings were not available and no mention was made of a postmortem examination, it is difficult to say whether intravenous pyelography had any role in inducing the uremia but the possibility cannot be excluded.

Perillie and Conn,[8] in discussing the mechanism of acute renal failure which occurred in the 5 cases reviewed by them, believe that precipitation of intratubular proteins is the main factor and they postulate that intravenous pyelography may set the stage for this precipitation in the following way. Cleansing cathartics and enemas preparatory to examination produce dehydration which is considerably increased by fasting and withdrawal of fluids. Dunbar, MacEwan and Hebert,[10] in a comprehensive study performed on normal male adults and experimentally in rabbits, recently demonstrated that there is a slight and consistent improvement in the quality of the intravenous pyelograms following dehydration, due to increased urinary concentration. Abdominal compression to block the flow of the contrast containing urine reduces renal blood flow and thereby further increases the urinary concentration, thus enhancing the precipitation of the abnormal proteins within the tubules. The plugging of the lower nephron then swiftly leads to obstructive uropathy, with oliguria, anuria and death.

Although the cited cases may appear unusual and may represent rare instances in the large number of intravenous pyelographic examinations performed routinely, certain precautions are definitely warranted. These are: Intravenous pyelography should not be performed in frank cases of multiple myeloma for any reason. In the occult cases of multiple myeloma, a diligent search should be made for protein abnormalities by electrophoretic studies of the blood serum and urine and, if their presence is demonstrated, intravenous pyelography should be omitted. In the cases of proteinuria of undetermined cause, the possibility of a multiple myeloma "masquerading" under the guise of a nephropathy should be kept in mind and intravenous pyelography performed only after the elimination of this possibility.

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[9] Pendergrass, E. P., Hodes, P. J., Tondreau, R. L., Powell, C. C., and Burdick, E. D. Further considerations on deaths and unfavorable sequelae following the administration of contrast media in urography in the United States. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1955, *74*, 262–287.

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NATIONAL COMMITTEE ON RADIATION PROTECTION AND MEASUREMENTS

A NUMBER of actions and activities of the NCRP and its subcommittees seem to be worthy of note at this time.

Just recently two new organizations have been accepted as sponsors. These are the American Nuclear Society and the Genetics Society of America. The NCRP is very happy, indeed, to have these two organizations assist in its programs.

Another action taken recently involved the reactivation of Subcommittee 1. This subcommittee under the chairmanship of H. H. Parker met on October 18, 1960 and began an active program, reflecting its concern with the development of the basic concepts and philosophy of radiation protection. The subcommittee decided to operate under a pattern that has been found to be successful with other subcommittees. It will have a small working group assisted by an advisory group or consultants as circumstances demand. The initial membership includes: H. M. Parker, Chairman, R. H. Chamberlain, J. F. Crow, H. Curtis, H. F. Friedell, H. J. Muller, C. Powell, H. H. Rossi.

Subcommittee 14 on "Permissible Exposure Doses under Emergency Conditions" under the chairmanship of G. V. LeRoy has been very active of late. A report of the subcommittee directed particularly to the problems of civil defense officials is now nearing completion and is expected to be submitted to the NCRP Main Committee in the near future.

Subcommittee M-4 on "Relative Biological Effectiveness" now under the chairmanship of V. P. Bond has also begun a very active program. They have outlined a method of approach for their program and begun preliminary work on a report. Arrangements have been made for liaison between this subcommittee and the joint ICRU-ICRP group concerned with similar problems.

Two new handbooks have been released during recent months and a number of others are now nearing completion. Handbook 72 on "Measurement of Neutron Flux and Spectra for Physical and Biological Applications" was released on July 15, 1960. Handbook 73 on "Protection Against Radiations from Sealed Gamma Sources" was released on July 27, 1960. Handbook 75 on "Measurement of Absorbed Dose of Neutrons and Mixtures of Neutrons and Gamma Rays" and Handbook 76, "Medical X-rays Protection up to Three Million Volts" (Revision of Handbook 60), are now at the printers and should be released soon. Two other handbooks are now undergoing editorial review and it is hoped that they, too, can soon be released. These are: "Stopping Powers for Use with Cavity Chambers" and "A Manual of Radioactivity Procedures."

REPORT OF THE INTERNATIONAL COMMISSION ON RADIOLOGICAL UNITS AND MEASUREMENTS

COMMITTEE ON THE METHODS OF RADIOLOGICAL EQUIPMENT AND MATERIALS

Subcommittee on Focal Spots

METHOD OF FOCAL SPOT IMAGE AND MEASUREMENT

(For Diagnostic Tubes Up to 150 Kev)

At the 1956 meetings of the International Commission on Radiological Units and Measurements, a new committee was established to study methods of evaluating radiological equipment and materials; it operates under the Chairmanship of Dr. B. Combee of the Netherlands with Dr. E. D. Trout of the U.S.A. as Vice-Chairman. A series of subcommittees have been set up to deal with specialized subjects. The report to follow is the first of the subcommittee reports to be completed.

As problems of radiation units and measurements have developed during recent years it has become increasingly evident that it is not feasible for the ICRU to publish a regular triennial report covering all areas of interest to the Commission. Therefore, it has been decided that as different committees or subcommittees of the Commission complete their reports they will be released for whatever journal publication may appear to be appropriate. Approximately every three years the committee will endeavor to compile as many of these reports as possible into a single report. By this procedure it is hoped to avoid holding up the release of one completed study, simply to have it included in a single report with all other studies.

This report of Subcommittee IV of the ICRU is the first such report to be released in the manner described above. It will also be included as Appendix II in the triennial report of the ICRU due for publication within a few months.

Committee IV of the ICRU consists of the following members: B. Combee, Chairman, Netherlands; E. Dale Trout (Vice Chairman), U.S.A.; E. Zieler (Technical Secretary), Germany; H. Berger, Germany; Bernard O'Loughlin, U.S.A.; A. S. Johnstone, England; J. Massiot, France; D. J. Stevens, Australia; S. W. Smith, U.S.A.; C. W. Wegelius, Sweden.

The Subcommittee (IV-1) that prepared this specific report consists of the following members: T. Rogers (Chairman), U.S.A.; G. M. Ardran, England; E. Fenner, Germany; R. Griffoul, France; A. Kuntke, Germany.

This report has been reviewed and approved by the ICRU.

Lauriston S. Taylor, Chairman

METHOD OF FOCAL SPOT IMAGE AND MEASUREMENT

Introduction

Report of the International Commission on Radiological Units and Measurements Subcommittee IV-1 on Focal Spots

The task of this Subcommittee has been considerably simplified by the instruction given to it in the report of ICRU IV dated August 14, 1958, as follows:

"Only the tools for making an accurate measurement under any desired operating conditions should be specified. The specification of tolerances allowable from nominal focal sizes, of the tube current and voltage conditions should be considered to be outside the scope of ICRU IV."

Consistent with this instruction, the Subcommittee has given special attention to methods of measurement of focal spot size in X-ray tubes for diagnosis. In this report we submit our recommendations for a measurement method and procedure suitable for such tubes, particularly of the line

focus variety, when operated at voltages not exceeding 150 kvp.

At the ICRU meeting held in Geneva, September, 1958, it was suggested that Subcommittee I should also include in its task the method of measurement of uniformity of focal spots and that the studies should not be limited to diagnostic tubes but should include therapy tubes and possibly radioactive sources. The Subcommittee has not as yet been able to evaluate this suggestion. It is of the opinion, however, that a method applicable specifically for diagnostic tubes can and should be recommended at this time, and that therapy tubes and radioactive sources should be the subject of further deliberation.

The following recommendations represent a composite of the positions taken by the individual members of the Subcommittee with respect to the various points involved rather than the unanimous opinion of all. However, a majority are in agreement that the method proposed will give a substantially accurate measure of the effective focal size of an X-ray tube under the operating conditions obtained at the time the measurement is made.

RECOMMENDATIONS

Method of Focal Spot Image Formation and Measurement

(For diagnostic tubes at voltages up to 150 kvp.)

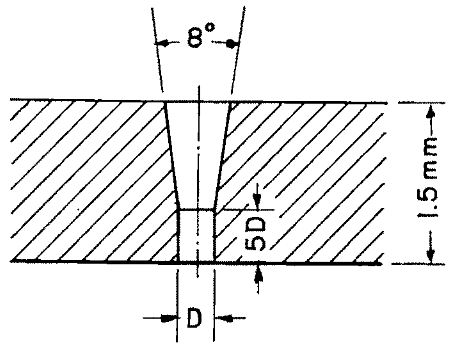
1. *Basic method*

Pinhole radiograph of focal spot, produced by pinhole accurately aligned with respect to "central ray" of X-ray beam.

2. *Details of pinhole camera*

a. Pinhole diameter: .030 mm. for focal sizes below 1.0 mm.; .075 mm. for focal sizes 1.0 mm. to 2.5 mm.; .100 mm. for focal sizes above 2.5 mm.

b. Diaphragm thickness, material, and pinhole profile: The pinhole diaphragm shall be manufactured from a 90/10 gold-platinum alloy, 1.5 mm. thick. The cylindrical part of the pinhole shall be five times as long as its diameter and followed by a conical part with a divergent angle of 8° (see diagram below).



c. Focal spot to pinhole distance: 10 cm. minimum (where focus location is not precisely known or directly measurable, precise location stereoscopically with dual pinholes is recommended).

d. Enlargement factor: 2.0 minimum for focal sizes up to 2.5 mm.; 1.0 minimum for focal sizes above 2.5 mm.

3. *Photographic technique*

a. Type of film: Any commonly used dental film (single coating).

b. Image density: 0.6 to 1.0, as measured in the most dense portion of the image. Density to be controlled by means of standard developing technique and proper exposure time at tube current and voltage factors employed. (This element involves a point of special difficulty, because of variations in structure of respective focal spots. If lines in focal spot are superimposed, greater maximum density results than in cases where lines are not superimposed, for equal exposure values. Hence a wide latitude in allowable maximum density become necessary.)

4. *Measurement of image*

a. Lighting: Back-lighted at approximately 20 foot-candles.

b. Measurement procedure: Use scaled magnifier with 0.1 mm. scale divisions, 5 to 10 times magnification. Measure length and width, respectively, including all perceptible portions of the image, to nearest 0.1 mm. For irregularly shaped (non-

rectangular) focal spots, measurement should be taken of all significant dimensions.

c. Correction of image measurements: All image dimensions shall be divided by the enlargement factor, accurately determined (see 2d).

5. *Statement of dimensions*

a. Width of focal spot shall be stated as the width of the image divided by the enlargement factor.

b. Length of focal spot shall be stated as the length of the image divided by the enlargement factor, further corrected by a multiplier of 0.7.[a]

c. For non-rectangular focal spots, all significant dimensions, including maximum diameter, shall be stated as indicated by actual measurements divided by the enlargement factor.[b]

[a] See Appendix A for explanation.

[b] See Appendix B for explanation.

APPENDIX A

The proposal of a fractional multiplier for correction of the measured image length arises from the long-recognized fact that the lengthwise distribution of energy in the focal spot of a line-focus tube tends to be peaked at the center and diminishes gradually to zero at the ends. Hence, the effective length, based on its effect on either radiographic definition or loading capacity, cannot be stated as equal to the measured image length as initially corrected. Some further correction is necessary. This point has been exposed, and to some extent explored in the papers heretofore presented by Polansky and O'Conner[1] (1954), Rogers[2] (1956), Fenner and Jochim[3] (1957), and Servais,[4] (1958). However, we do not feel that work done to date has been sufficiently comprehensive to establish a suitable correction factor, and the suggestion above of a multiplier of 0.7 is given primarily by way of example or as an approximate value rather than as a final recommendation. We would like to recommend that ICRU IV enlist the good offices of a suitable research organization to explore this matter quantitatively over the entire range of diagnostic tubes commercially produced, with the objective of establishing a proper formula for focal spot length.

APPENDIX B

Off-Focus Radiation

It must be recognized that the effect of any off-focus radiation on definition is not taken into account by these measurements, and unless off-focus radiation is suppressed, the definition to be expected from the tube may be influenced by it.

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SOCIETY PROCEEDINGS AND NEWS ITEMS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Deauville Hotel, Miami Beach, Fla., Sept. 26–29, 1961.

AMERICAN RADIUM SOCIETY
Secretary, Dr. Charles G. Stetson, 350 Engle Street, Englewood, N. J. Annual meeting: Broadmoor Hotel, Colorado Springs, Colo., May 11–14, 1961.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Maurice Doyle Frazer, 1037 Stuart Bldg., Lincoln, Neb.
Treasurer, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual meeting: to be announced.

AMERICAN COLLEGE OF RADIOLOGY
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: Chicago, Ill., Feb. 8–11, 1961.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: New York City, June 26–30, 1961.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building. Rochester, Minn. The Spring 1961 examination will be held at the Denver Hilton Hotel, Denver, Colorado, June 19–22, inclusive; the deadline for filing applications was January 1, 1961. There will be no Special Examination in Nuclear Medicine. The Fall 1961 examination will be held at the Shoreham Hotel, Washington, D. C., December 4–7, inclusive; the deadline for filing applications is July 1, 1961. A Special Examination in Nuclear Medicine will be offered if there are sufficient applications.

TENTH INTERNATIONAL CONGRESS OF RADIOLOGY
Secretary-General, Dr. Carleton B. Peirce, Royal Victoria Hospital, Montreal 2, Quebec, Canada. Meets in Montreal, Aug. 26–Sept. 1, 1962.

SEVENTH INTER-AMERICAN CONGRESS OF RADIOLOGY
Counselor for the United States, Dr. J. A. del Regato, Penrose Cancer Hospital, 2200 North Cascade Avenue, Colorado Springs, Colorado. The meeting will be held in São Paulo, Brazil, September 3–10, 1961.
Secretary-General, Dr. Walter Bomfim-Pontes, Rua Cesario Motta, No. 112, São Paulo.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

AMERICAN NUCLEAR SOCIETY
Executive-Secretary, Octave J. Du Temple, 86 E. Randolph St., Chicago, Ill.

ARIZONA RADIOLOGICAL SOCIETY
Secretary, Dr. Don E. Matthieson, 926 East McDowell Rd., Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. J. B. Scruggs, Arkansas Baptist Hospital, Little Rock, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary, Dr. Melvin M. Figley, Department of Radiology, University of Washington, Seattle 5, Wash. Annual meeting to be announced.

ATLANTA RADIOLOGICAL SOCIETY
Secretary, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

BLOCKLY RADIOLOGICAL SOCIETY
Secretary, Dr. Samuel Finkelman, 101 S. Twentieth St. Philadelphia, Pa.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph Arcomano, 168 Clinton St., Brooklyn 1, N. Y. Meets first Thursday of each month October through May.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Kenneth H. Seagrave, 537 Delaware Ave., Buffalo 2, N. Y. Meets second Monday evening each month, October to May inclusive.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph A. Head, 150 Marshall St., Syracuse, N. Y. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. Robert L. Freidman, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL SOCIETY OF NUCLEAR MEDICINE
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. William F. Hutson, 5145 N. California Ave., Chicago, Ill. Meets second Thursday of each month, October to April except December at the Sheraton Hotel at 8:00 P.M.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. Norman E. Berman, 14404 S. Park Blvd., Shaker Hgts. 20, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

COLORADO RADIOLOGICAL SOCIETY
Secretary, Dr. Bertram L. Pear, 3705 East Colfax Ave., Denver 6, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY
Secretary, Dr. Paul J. Kingston, 114 Woodland St., Hartford, Conn. Meets first Friday in February and April.

DALLAS-FORT WORTH RADIOLOGICAL CLUB
Secretary, Dr. W. H. Neil, 1217 W. Cannon St., Fort Worth, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit 1, Mich. Meets monthly first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

EAST BAY ROENTGEN SOCIETY
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

EAST TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. J. Marsh Frere, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.

EASTERN CONFERENCE OF RADIOLOGY
Secretary, Arrangements Committee, Dr. Philip Myers, Baltimore City Hospital, Baltimore 24, Md. Annual meeting: Lord Baltimore Hotel, Baltimore, Md., March 9–11, 1961.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Eastern Radiological Society
Secretary, Dr. John D. Osmond, Jr., Euclid-Glenville Hospital, Cleveland 19, Ohio. Meets at Mid Pines Club Southern Pines, N. C., April 16–19, 1961.

Florida Radiological Society
Secretary, Dr. John P. Ferrell, 166 4th Ave., St. Petersburg, Fla. Meets twice annually, in the spring with the annual State Society Meeting, and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.

Georgia Radiological Society
Secretary, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Miami Radiological Society
Secretary, Dr. Donald H. Altman, 2751 Coral Way, Miami, Fla. Meets monthly third Wednesday at 8 p.m. at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Radiological Society
Secretary, Dr. Harvey A. Humphrey, 462 N. Taylor, St. Louis 8, Mo.

Houston Radiological Society
Secretary, Dr. Edward B. Singleton, 6621 Fannin St., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.

Idaho State Radiological Society
Secretary, Dr. Claude W. Barrick, St. Alphonsus Hospital, Boise, Idaho. Meets in the Spring and Fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. David E. Wheeler, 1500 North Ritter, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary, Dr. Lewis G. Allen, 807 Huron Bldg., Kansas City, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. Robert H. Akers, V. A. Hospital, Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 p.m.

Los Angeles Radiological Society
Secretary, Dr. Walter Stilson, 1720 Brooklyn Ave., Los Angeles, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. Albert A. Poulin, Thayer Hospital, Waterville, Maine. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

Memphis Roentgen Society
Secretary, Dr. Hollis H. Halford, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. S. F. Johnson, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 p.m., fourth Wednesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. Joseph F. Wepfer, 5000 W. Chambers St., Milwaukee 10, Wis. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.

Mississippi Radiological Society
Secretary, Dr. Bernard T. Hickman, University Medical Center, Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 p.m.

Montana Radiological Society
Secretary, Dr. J. K. Boughn, 35 11th Ave., Helena, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Alan E. Baum, 100 Nowbridge Rd., Hicksville, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. Ronald E. Waggener, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Nebraska. Meets third Wednesday of each month at 6 p.m. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through May at The Longwood Towers, Brookline, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Albert A. Dunn, 622 W. 168th St., New York, N. Y. Meets monthly on third Monday, New York Academy of Medicine at 4:30 p.m.

North Carolina Radiological Society
Secretary, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. R. F. Raasch, Post Office Box 990, Dickinson, North Dakota. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Paul A. Mori, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Lester I. Citrin, St. Mary's Hospital, Troy, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. Paul D. Meyer, 125 S. Grant Ave., Columbus, Ohio. Annual meeting third week end in May, 1961 at Columbus, Ohio.

Oklahoma State Radiological Society
Secretary, Dr. E. D Greenberger, Medical Arts Bldg., McAlester, Okla. Meets in January, May and October.

Oregon Radiological Society
Secretary, Dr. George R. Satterwhite, 1123 S.W. Yamhill, Portland, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 p.m. at the University Club.

ORLEANS PARISH RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY
Secretary, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Portland, Oregon, May, 1961.

PACIFIC ROENTGEN SOCIETY
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

PENNSYLVANIA RADIOLOGICAL SOCIETY
Secretary, Dr. Frederick R. Gilmore, 234 State St., Harrisburg, Pa. Annual meeting: Bedford Springs Hotel, May 26–27, 1961.

PHILADELPHIA ROENTGEN RAY SOCIETY
Secretary, Dr. Robert B. Funch, Department of Radiology, Germantown Hospital, Philadelphia 44, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY
Secretary, Dr. Ross H. Smith, St. Margaret Memorial Hospital, Forty-Sixth St., Pittsburgh 1, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

RADIOLOGICAL SECTION, BALTIMORE MEDICAL SOCIETY
Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI
Secretary, Dr. Donald Janny, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

RADIOLOGICAL SOCIETY OF HAWAII
Secretary, Dr. Philip S. Arthur, 274 Young Hotel Bldg., Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

RADIOLOGICAL SOCIETY OF KANSAS CITY
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA
Secretary, Dr. Robyn Hardy, 4324 Magnolia St., New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

RADIOLOGICAL SOCIETY OF NEW JERSEY
Secretary, Dr. Austin J. Tidaback, 912 Prospect Ave., Plainfield, N. J. Meets at Atlantic City at time of State Medical Society meeting and in November in Newark, N. J.

RADIOLOGICAL SOCIETY OF NEW YORK STATE
Secretary-Treasurer, Dr Mario C. Gian, 610 Niagara St., Buffalo 1, N. Y. Annual meeting to be announced.

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA
Secretary, Dr. Joseph F. Linsman, 436 N. Roxbury Dr., Beverly Hills, Calif.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.
Secretary, Dr. Robert H Greenlaw, 188 Irvington Rd., Rochester 20, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: Denver Hilton Hotel, Denver, Colo., Aug. 10–12, 1961.

SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

SAN DIEGO RADIOLOGICAL SOCIETY
Secretary, Dr. Stanley A. Moore, 2466 First Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

SAN FRANCISCO RADIOLOGICAL SOCIETY
Secretary, Dr. M. A. Sisson, 450 Sutter St., San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

SECTION ON RADIOLOGY, CONNECTICUT STATE MEDICAL SOCIETY
Secretary, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bi-monthly.

SECTION ON RADIOLOGY, MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA
Secretary, Dr. William E. Sheely, 1746 K St., N.W., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY
Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION
Secretary. Dr. Seymour Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La. Annual meeting to be announced.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY
Secretary, Dr. Richard G. Lester, 412 Union St., S.E., Minneapolis 14, Minn. Annual meeting: Deaville Hotel, Miami Beach, Fla., Sept. 25, 1961.

SOCIETY OF NUCLEAR MEDICINE
Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. *Administrator*, Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Penn Sheraton Hotel, Pittsburgh, Pa., June 14–17, 1961.

SOUTH BAY RADIOLOGICAL SOCIETY
Secretary, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

SOUTHERN RADIOLOGICAL CONFERENCE
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, Mobile, Ala.

SOUTHWESTERN RADIOLOGICAL SOCIETY
Secretary, Dr. Ralph S. Clayton, 1501 Arizona, Bldg. 2-A, El Paso, Texas. Meets second Tuesday of each month.

TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. James J. Range, P.O. Box 324, Johnson City, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS RADIOLOGICAL SOCIETY
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Texas. Next meeting January 20 and 21, 1961, Texas Hotel, Fort Worth, Texas.

Tri-State Radiological Society
Secretary, Dr. James R. Mathews, 118 S. E. First St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
Secretary, Dr. Frank A. Kearney, II, 110 S. Curry St., Phoebus, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Joseph T. Houk, 14303 Ambaum Blvd., Seattle 66, Wash. Meets third Monday of each month from September through April at the University of Washington Medical School.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, 112 N. Woods St., Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Richard P. Avondu, Yonkers General Hospital, Park & Ashburton Ave., Yonkers, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Howard G. Bayley, 116 Iroquois Parkway, Beaver Dam, Wis. Annual meeting each spring in various places.

X-Ray Study Club of San Francisco
Secretary, Dr. John H. Heald, 450 Sutter St., San Francisco 8, Calif. Meets monthly, third Thursday at 7:30 P.M., Children's Hospital, September through June.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Julio Toriello, 11 Calle 2-37, zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Rafael Vega Gómez.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15, México 7, D. F.
Secretary-General, Dr. E. Alvarez Hernández. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
Secretary, Dr. Odilon Raymond, 5400 Blvd. Gouin. Quest, Montreal, Que. Meets four times a year.

British Institute of Radiology Incorporated with the Röntgen Society
Honorary Secretary, Dr. John Blewett, 32 Welbeck St., London, W. 1. Meets monthly from October until May.

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting to be announced.

Section of Radiology of the Royal Society of Medicine ((Confined to Medical Members),
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1.

Canadian Association of Radiologists
Honorary Secretary, Dr. Robert G. Fraser, *Associate Honorary Secretary*, Dr. Jean-Louis Léger, 1555 Summerhill Ave., Montreal 25, Que. Annual meeting: January 22–25, 1961, Saint John, New Brunswick.

Montreal Radiological Study Club
Secretary, Dr. F. McConnell, 1650 Cedar Ave., Montreal, Quebec. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
General Secretary, Dr. Louis Ivan Vallée, 1058 rue St-Denis, Montreal 18, Canada. Meets third Saturday each month.

Toronto Radiological Society
Secretary, Dr. L. R. Harnick, Toronto Western Hospital, 399 Bathurst St., Toronto, Ontario. Meets second Monday of each month September through May.

College of Radiologists of Australasia
Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, D. Camillo Segreto, Avenida Angélica, 1.170, Caixa Postal 5984, São, Paulo, Brazil.

Sociedad Argentina de Radiología, Junta Central Buenos Aires
Secretary, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25–31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Perú. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris.
Secretary-General, Dr. Ch. Proux, 9, rue Daru, Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut. Lagenbeckstr. 1, Mainz, Germany. Annual meeting: April 12–15, 1961.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Electrologie en Röntgenologie
Secretary, Dr. J. R. von Ronnen, Violenweg 14, den Haag Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The next list of Meetings of Radiological Societies will be published in the March, 1961 issue of the Journal.

THIRTEENTH ANNUAL MIDWINTER RADIOLOGICAL CONFERENCE

The Thirteenth Annual Midwinter Radiological Conference, sponsored by the Los Angeles Radiological Society, will be held at the Biltmore Hotel, Los Angeles, California, on Saturday and Sunday, January 28 and 29, 1961.

An outstanding program of pertinent interest has been arranged and the guest speakers will be Dr. James W. D. Bull, London, England; Dr. John Boland, New York, New York; Dr. John A. Kirkpatrick, Philadelphia, Pennsylvania; and Dr. John F. Holt, Ann Arbor, Michigan.

The conference fee of $20.00 includes two luncheon meetings featuring questions and answers. A banquet ($7.50 per plate) preceded by cocktails will be held Saturday evening. Reservations may be made through: Joseph Parks, M.D., 14500 Sherman Circle, Van Nuys, California.

Courtesy cards will be available to residents in Radiology and Radiologists in the Armed Forces by advance registration, with reduced rates for the luncheons and banquet. Hotel reservations should be made promptly through the Convention Manager, Biltmore Hotel, Los Angeles, Calif.

EASTERN CONFERENCE OF RADIOLOGY

The annual meeting of the Eastern Conference of Radiology will be held March 9–11, 1961, at the Lord Baltimore Hotel, Baltimore, Maryland. The Secretary of the Arrangements Committee is Dr. Philip Myers, Baltimore City Hospital, Baltimore 24, Maryland.

COURSE IN CLINICAL USE OF RADIOACTIVE ISOTOPES

A course in the clinical use of radioactive isotopes will be given under the supervision of Dr. Sergei Feitelberg and Dr. Edith Quimby of the Department of Radiology, Columbia University, New York City, from June 5 through June 30, 1961. This is a full-time course which includes lectures, experimental laboratory exercises, clinical rounds and clinical measurements on patients and on specimens. In addition to Drs. Feitelberg and Quimby, the teaching staff will comprise sixteen invited lecturers from the New York area, each presenting material in his own special field.

Enrollment in the class is limited to 20; the fee is $300.

Inquiries should be addressed to Dr. Sergei Feitelberg, Mt. Sinai Hospital, Fifth Avenue at 100th Street, New York, N.Y.

COURSE IN RADIOLOGY AND RADIOACTIVE ISOTOPES

A three-day postgraduate course in Radiology and Radioactive Isotopes has been announced for February 20, 21, and 22, 1961 at the University of Kansas Medical Center, Kansas City, Kansas. A guest faculty of eight nationally recognized authorities will present didactic material.

Information concerning the program and registration may be had by writing the Department of Postgraduate Medical Education, The University of Kansas School of Medicine, Kansas City 12, Kansas.

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Forty-sixth Annual Meeting of the Radiological Society of North America held at the Netherland Plaza Hotel, Cincinnati, Ohio, December 4–9, 1960, the following officers were elected: President, M. Milton Berg, Bismarck, North Dakota; President-Elect, Charles McCurdy Gray, Tampa, Florida; First Vice President, Philip J. Hodes, Philadelphia, Pennsylvania; Second Vice President, John R. Hodgson, Rochester, Minnesota; Third Vice President, George Cooper, Jr., Charlottesville, Virginia; New Member of Board of Directors, John William Walker, Kansas City, Missouri; Secretary, Maurice Doyle Frazer, Lincoln, Nebraska; Treasurer, Dwight Vincent Needham, Syracuse, New York; and Historian, Howard P. Doub, Detroit, Michigan.

Drs. Thomas Burke Bond, Fort Worth, Texas and Warren H. Cole, Chicago, Illinois, were awarded the Gold Medal, highest honor of the Society. Dr. Howard P. Doub was presented with a beautiful silver platter "in appreciation of twenty years of loyal service as Editor of *Radiology*."

BOOKS RECEIVED

Comparative Effects of Radiation; Report of a Conference held in San Juan at the University of Puerto Rico, February 15–19, 1960, sponsored by National Academy of Sciences—National Research Council. Edited by Milton Burton, Chemistry Department and Radiation Laboratory, University of Notre Dame; J. S. Kirby-Smith, Biology Division, Oak Ridge National Laboratory; and John L. Magee, Chemistry Department and Radiation Laboratory, University of Notre Dame. Cloth. Price, $8.50. Pp. 426. John Wiley & Sons, Inc., 440 Fourth Ave., New York 16, N. Y., 1960.

A Clinical Prospect of the Cancer Problem. Introductory Volume, Monographs on Neoplastic Disease. General Editor, D. W. Smithers, M.D., F.R.C.P., F.F.R., Professor of Radiotherapy in the University of London; Director, Radiotherapy Department, Royal Marsden Hospital, and Institute of Cancer Research, Royal Cancer Hospital; Radiotherapist, Brompton Hospital. Cloth. Pp. 232, with 46 illustrations. E. & S. Livingstone, Ltd., 16–17 Teviot Place, Edinburgh 1, Scotland, 1960.

Lumbar Discography and Low Back Pain. By Donald deForest Bauer, M.D., C.M., M.Sc., Consulting Radiologist, Klamath Valley Hospital and Hillside Hospital; Associate Supervisor and Radiologist, Department of Medical X-Ray Technology, Oregon Technical Institute, Klamath Falls, Oregon. Cloth. Price, $5.00. Pp. 89, with 32 illustrations. Charles C Thomas, Publisher, 301–327 E. Lawrence Ave., Springfield, Ill., 1960.

The Basic Physics of Radiation Therapy. By Joseph Selman M.D., Clinical Assistant Professor of Radiology, The Southwestern Medical School, University of Texas; Director, School of X-Ray Technicians, Tyler Junior College; Chief of Radiology Service, Medical Center Hospital; Attending Radiologist, Mother Frances Hospital; Consultant in Radiology, East Texas Tuberculosis Hospital, Tyler, Texas. Cloth. Price, $14.50. Pp. 671. Charles C Thomas, Publisher, 301–327 E. Lawrence Ave., Springfield, Ill., 1960.

Occupational Diseases and Industrial Medicine. By Rutherford T. Johnstone, M.D., Consultant in Industrial Medicine; Clinical Professor of Preventive Medicine and Public Health; Clinical Professor of Medicine, University of California at Los Angeles; and Seward E. Miller, M.D., Director, Institute of Industrial Health; Professor of Medicine, Medical School, University of Michigan; Professor of Industrial Health, School of Public Health, University of Michigan. Cloth. Pp. 482. W. B. Saunders Co., 218 W. Washington Square, Philadelphia 5, Pa., 1960.

Selected Papers from the Institute of Cancer Research: Royal Cancer Hospital and from the Royal Marsden Hospital—1958. Volume 13. Cloth. Pp. 1016. The Chester Beatty Research Institute, Fulham Road, London, S. W. 3, England, 1960.

The Normal Skull; A Roentgen Study. By Robert Shapiro, M.D., Chairman, Department of Radiology, Hospital of Saint Raphael, New Haven; Associate Clinical Professor of Radiology, Yale University School of Medicine; and Arnold H. Janzen, M.D., Assistant Radiologist, Hartford Hospital, Hartford; Former Chairman, Department of Radiology, Grace-New Haven Community Hospital and Yale University School of Medicine, New Haven. Cloth. Price, $18.00. Pp. 257, with 645 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, N. Y., 1960.

Die Chirurgie des Magensarkoms. By Prof. Dr. A Gütgemann, Direktor der Chirurgische, Universitätsklinik und Poliklinik, Bonn; and Dr. H. W. Schreiber, Wissenschaftl. Assistent an der Chirurgische, Universitätsklinik und Poliklinik, Bonn. Paper. Price, $6.80. Pp. 95, with 31 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart N, Germany, 1960. In the United States and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

Die occipitale Dysplasie. By Doz. Dr. H. Schmidt and Dr. E. Fischer, Medizinisches Strahleninstitut der Universität Tübingen. Paper. Price, $8.35. Pp. 69, with 69 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart N, Germany, 1960. In the United States and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

La Radiculographie Lombaire dans la Sciatique. By J. Ecoiffier, Radiologiste des Hôpitaux de Paris. Paper. Pp. 140, with 51 illustrations. Masson et Cie, Éditeurs, 120 Boulevard Saint-Germain, Paris 6e, France, 1960.

La Stratigrafia nella Patologia del Mediastino. By G. L. Besio; P. de Albertis; P. Pierotti; and M. Scursatone. Cloth. Price, L. 5,500. Pp. 254, with 171 illustrations. Società Editrice "Universo," Via G. B. Morgagni 1, Rome, Italy, 1960.

Modern Trends in Diagnostic Radiology (Third Series). Edited by J. W. McLaren M.A., M.R.C.P., F.F.R., D.M.R.E., Radiologist, X-Ray Department, St. Thomas' Hospital, London; Examiner in Radiology to the Examining Board of England and to Edinburgh University; sometime Examiner in Radiology, University of London and Faculty of Radiologists. Cloth. Price, $16.00. Pp. 285, with 209 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, N. Y., 1960.

Radiation Therapy of Early Prostatic Cancer. A Monograph in American Lectures in Urology. Publication number 399 in the American Lecture Series. By R. H. Flocks, M.D. and D. A. Culp, M.D., both of the State University of Iowa Department of Urology, Iowa City, Iowa. Charles C Thomas, Publisher, 301–327 E. Lawrence Ave., Springfield, Ill., 1960.

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. LEUCUTIA, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

NECK AND CHEST

BASU, S. P. Radiological appearance in the lung fields of tropical eosinophilia. *Calcutta M. J.*, May, 1960, *57*, 152–156. (From: School of Tropical Medicine, Calcutta, India.)

Tropical eosinophilia appears to be a clinical entity but the etiology is unknown. Roentgenologically it is identical with Loeffler's syndrome. The author studied the chest roentgenograms of more than 400 cases of tropical eosinophilia. The most common abnormality was an increase in the vascular markings. This occurred in 67 per cent of the patients and was usually associated with prominent hilar shadows. The next most common abnormality was a mottling of the lung fields, occurring in 31 per cent of the patients. The densities varied in size from 2 to 5 mm., were usually poorly circumscribed, and were irregular in outline. The author feels that a variation in the size of the densities is typical of tropical eosinophilia and helps differentiate it from other diseases such as sarcoidosis, pneumoconiosis, and miliary tuberculosis. Fine densities and large patchy shadows were uncommon. The lungs had a normal appearance in only 2 per cent of the patients with tropical eosinophilia.

The course of the disease was variable. Roentgen improvement tended to be slow and did not necessarily keep pace with the clinical improvement of the patient. In many instances follow-up roentgenograms showed a further increase in the abnormal densities, even though the patient had become symptom free and the eosinophil count was dropping. Improvement tended to occur first in the peripheral lung fields, while the prominent hilar shadows returned to normal more slowly or remained permanently enlarged. Only 25 per cent of the cases showed normal chest roentgenograms within six weeks. Recurrences of symptoms and roentgen abnormalities were common, even after a remission of months or years.—*F. L. Williams, M.D.*

FLAHERTY, ROBERT A., KEEGAN, JAMES M., and STURTEVANT, HARWOOD N. Post-pneumonic pulmonary pneumatoceles. *Radiology*, Jan., 1960, *74*, 50–53. (Address: R. A. Flaherty, Lutheran Hospital, Fort Wayne, Ind.)

The authors report 20 cases in which pulmonary pneumatoceles developed as a complication of pneumonia and they discuss the mechanism of development, the roentgen appearance and the ultimate prognosis. Eight of the reported cases were children and 12 were adults. The etiologic factor in most cases in both age groups was staphylococcal pneumonia.

The pneumatoceles are thin-walled, air-containing, cyst-like structures. They are believed to be the result of localized obstructive emphysema secondary to inflammatory narrowing of a bronchus. The most significant feature in patients with pulmonary pneumatoceles is the absence of symptoms after the pneumonia subsides and the pneumatocele remains. Eighteen of the 20 patients in the authors' series were completely asymptomatic at the time the pneumatocele was fully developed. When first identified, a pneumatocele appears as a small air space within the area of pneumonitis. As it enlarges, the wall may appear thick but the degree of thickness cannot be determined accurately because of the surrounding pneumonia. As the pneumonia resolves, the typical thin-walled cyst appears. The pneumatoceles may be single or multiple. They may contain fluid but usually are completely air-filled. Usually they disappear in a period of weeks or months following their onset, leaving a thin fibrotic strand in the area.

Pneumatoceles occurring in infants must be differentiated from congenital cysts of the lung and lobar emphysema. When a pneumatocele occurs in an adult, it may be confused with the thin-walled cavities which can occur in the mycotic infections. The clinical course and the recovery of *Staphylococcus aureus* in the early stage of the inflammatory process are the best means of differentiating pneumatoceles from cavities of a more serious nature.—*Arno W. Sommer, M.D.*

SCATLIFF, JAMES H., KUMMER, ALFRED J., and JANZEN, ARNOLD H. The diagnosis of pericardial effusion with intracardiac carbon dioxide. *Radiology*, Dec., 1959, *73*, 871–883. (Address: J. H. Scatliff, Yale-New Haven Medical Center, Hew Haven 4, Conn.)

The limitations of plain roentgenography, kymography, and fluoroscopy, and the added hazard when opaque angiography and pericardiocentesis are used to establish the diagnosis of pericardial effusion, are recognized. Intracardiac insufflation of carbon dioxide into the right atrium as a means of differentiating pericardial effusion from cardiac enlargement and pericarditis as reported by others has been evaluated in a group of 22 patients, correlating the findings with the clinical course or subsequent autopsy findings.

With the patient in the left lateral decubitus position, an injection of 50 to 100 cc. of gas is made over a two to three second interval into the antecubital vein. The carbon dioxide, once in the right atrium, rises and outlines its uppermost surface. The opaque shadow or band outlined between the carbon dioxide bubble and the overlying lung consists of pleura, pericardium, and atrial wall. The thickness of this band can then be recorded and measured by appropriate roentgenographic procedures. Normally the shadow should be no more than 5 mm. thick. In the presence of pericardial effusion, the heart assumes a dependent position and the fluid, if freely mobile and in sufficient quantity, widens the space

between the pericardium and atrium producing a widened opaque band. In the large dilated heart the right atrial wall remains of normal size or its thickness is only slightly increased. Therefore, it is possible in most instances to differentiate between cardiac enlargement and significant pericardial effusion; however, there is a zone, roughly between 5 and 20 mm., which may represent pericardial effusion, pericarditis, or both. Asymmetry of the opaque band suggests effusion, whereas constant uniform thickness of the opaque band and flattening of the dome of the gas bubble by the relatively inelastic pericardium indicate pericarditis. These findings are in general agreement with opaque angiographic studies reported by others.

Confusing shadows, unless recognized as such, may be produced by the presence of gas in the vena cava and hepatic veins, the opaque density of the blood-filled left atrium overlying the right atrial gas shadow, the appearance of a compartmentalized gas shadow due to some of the gas collecting in a smaller volume of atrium above the crista terminalis, the appearance of a heavily trabeculated atrial appendage, the presence of a gas bubble under a tricuspid valve in the right ventricle, and the presence of the shadow of a superimposed intermediate bronchus or ramifying pulmonary vessels. Pericardial disease such as benign or malignant tumors, metastases, multiple myeloma, sarcoidosis, or amyloid infiltration, if present in the region of the right atrial wall, may displace the gas bubble, giving a false positive finding of fluid. Lesions within the right atrium such as tumor or thrombus will also produce an abnormal outline in the opaque band. In such cases opaque contrast studies may be indicated, where opacification of all the cardiac chambers will give more information regarding the extent of the lesion than the localized carbon dioxide study. Pulmonary infiltration in the vicinity of the right atrium or mobile right pleural fluid will obviate accurate assessment of the opaque band.

Initially the patients were turned into the supine position at the conclusion of the examination, usually twenty to thirty seconds after the injection. One of the 15 patients manipulated in this fashion developed an episode of paroxysmal coughing lasting for thirty minutes. This was the only one in the entire series in whom any complication was manifested The results of experimental studies on two dogs in which the nitrogen content of the bubble and femoral artery pressures were measured seem to indicate the possibility of embolism or hypotensive effects developing when the patient is turned on his back. Consequently the patients are now maintained in the left decubitus position after injection until complete resorption of the gas bubble has been checked after five minutes.

Possibly the only contraindication to carbon dioxide examination is the presence of a known large intracardiac shunt; however, even this is doubtful. A further limitation of the technique is the necessity of placing the patient in the left decubitus position and maintaining that posture for at least ten minutes. If chronic lung disease or congestive failure is present, a preliminary trial in the left decubitus position may be made to check for development of unusual pulmonary symptoms.

Several case reports are presented to illustrate the value of this procedure.—*Walter H. Jarvis, Jr., M.D.*

Abdomen

Hiemsch, W. Zur Methodik der röntgenologischen Funktionsprüfung operierter Mägen. (A method for roentgen study of gastric function in the postoperative stomach.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1960, *92*, 395–401. (Address: Ev. Diakonissenanstalt, Hemmstr. 124/126, Bremen, Germany.)

Roentgen observation of 55 patients with gastroenterostomies showed that ordinary barium passed rapidly through the gastric stump and resulted in an inadequate study of the function of the gastroenterostomy. When the following mixture was used—1 slice of white bread (about 50 gm.) in 100 cc. of milk and barium sulfate suspension ad 200 gm.—the appearance of the gastric stump was markedly changed. It became dilated like an atonic balloon and then emptied slowly in gradual spurts, so that the outline and mucosal pattern of the gastric stump as well as the proximal small bowel could be satisfactorily studied. Thus the mixture more closely approximates the conditions that obtain when food is taken. Fewer cases of "dumping" were found with this method.—*J. Zausner, M.D.*

Pyle, Roger, and Samuel, Eric. An evaluation of the hazards of barium enema examinations. *Clinical Radiology*, July, 1960, *11*, 192–196. (From: Department of Diagnostic Radiology, Royal Infirmary, Edinburgh, Scotland.)

The widespread use of barium enema examinations has resulted in such familiarity with the procedure that a false sense of security has developed; a careful appraisal of the potential dangers of the investigation is made all too infrequently. As the examination is extensively used for exclusion of malignant disease, it naturally follows that many of the patients are elderly and frail and this in itself constitutes a special hazard.

Injury to the bowel wall from an incorrectly inserted enema tube is the most common complication. The only tube which should be inserted blindly into the rectum is a soft rubber one, and even this has been reported to perforate apparently healthy bowel. Where there is a colostomy, it may be necessary to administer the enema through it, and this is

another potential source of danger, as damage to the colon and perforation are more frequent in these cases than in a normal rectum. Safeguards against perforation are: the use of a rubber catheter, the use of a teat from a feeding bottle, to which the catheter is threaded and which is kept centrally in the stoma, the avoidance of force with the removal and reinsertion of the tube should any difficulty be encountered, and insertion of the catheter to the minimum distance compatible with adequate filling. Under normal circumstances, using the gravity tank method of administration with the can at three feet, perforation from hydrostatic pressure may only occur in a diseased bowel. The high mortality associated with perforation should be an adequate warning against the temptation to raise the fluid reservoir higher to obtain a more rapid flow.

Another serious complication of the enema is "water intoxication." Water retained or absorbed without electrolyte can lower the osmolarity of the body fluid and cause severe symptoms which are mainly cerebral. Water intoxication has been not infrequently reported in cases of megacolon, and there have been several fatalities reported. Prevention of water intoxication by raising the osmotic pressure of the administered fluid by the addition of salt has been recommended and is simple to do; also, a saline solution is considered to be simple and safe in the absence of renal and cardiac insufficiency. Barium enema in megacolon should be allowed to proceed only until the dilated segment is reached, at which stage the enema should be stopped.

In a large series of barium enema examinations investigated by Zhentlior, Lassar and Rigler, perforation of the bowel was found to occur relatively more frequently under three circumstances: (1) when the enema was performed by way of a colostomy stoma; (2) when an inflatable balloon was used; and (3) when the examination followed shortly after endoscopy. Intestinal obstruction due to the impaction of barium sulfate and feces into hard masses occasionally occurs. Ulcerative colitis carries a greater risk of perforation of the bowel, and barium enema in this condition should be most carefully and slowly administered. The use of a self-retaining inflatable Foley catheter counteracts leakage of the fluid from the rectum during the filling, but the air pressure should not exceed 25 mm. Hg within the bag. With the addition of tannic acid to the enema fluid to promote good evacuation for a mucosal relief study, concentrations of 0.5 per cent have given rise to abdominal pain and colic, and a concentration of 1.0 per cent has been followed by vasomotor collapse and shock.

Brown and Fine in 1941 reported an unusual complication when, during air insufflation for double contrast, air was seen to enter the retroperitoneal space. Retrosternal mediastinal emphysema and surgical emphysema in the neck developed, but the symptoms and signs cleared completely several days later. The authors report a similar case in which little or no air remained in the bowel lumen, most of it accumulating in the retroperitoneum. Twelve hours later surgical emphysema was noted in the neck and roentgenograms revealed a retroperitoneal pneumogram. Air was present under the diaphragm and in the mediastinum and neck. On sigmoidoscopy, at 10 cm. there was a small area of proctitis, which, in the opinion of the endoscopist, was compatible with a perforation of the posterior rectal wall at this point. However, the collapsed mucosal pattern of the rectum on the insufflation roentgenogram suggested that perforation had occurred within 5 cm. of the anus. Uneventful recovery occurred.—*Samuel G. Henderson, M.D.*

BRUNTON, F. J. Retroperitoneal emphysema as a complication of barium enema. *Clinical Radiology*, July, 1960, *11*, 197–199. (From: The Diagnostic Radiological Department, St. Mary's Hospital, London, W.2, England.)

The better known complications of barium enema examination include intraperitoneal perforation of the bowel, fatal intravasation, water intoxication and barium granulomata of the rectum. Retroperitoneal emphysema, although less well known, is a recognized complication of sigmoidoscopy and of rectosigmoid surgical operations. The author describes a case of widespread interstitial emphysema following air insufflation in an elderly woman with diverticulitis.

The air leakage occurred during the insufflation, but the exact site was not ascertained. The possibility of rectal injury by the nozzle of the syringe or by a balloon obturator (used to retain the barium enema) is considered. Another possibility is that a diverticulum or mural abscess was perforated low in the sigmoid. Retroperitoneal emphysema developed and air was present in the perirectal area. Later, subcutaneous emphysema was noted in the upper chest and neck, and air was seen also in the mediastinum. The patient was treated with intramuscular penicillin and streptomycin initially, and later with oral terramycin. She remained afebrile and the air was gradually absorbed within a period of a week. She suffered no other ill effects.—*Samuel G. Henderson, M.D.*

ELSON, MATTHEW W. Antemortem radiographic demonstration of gas gangrene of the liver. *Radiology*, Jan., 1960, *74*, 57–60. (Address: University Hospital, 11th and Neil Aves., Columbus 10, Ohio.)

The author presents what appears to be the first reported case of gas gangrene of the liver with positive roentgenographic findings observed before death. The patient's clinical history and the physical and autopsy findings are described in detail. Posteroanterior roentgenograms of the chest and a supine roentgen examination of the abdomen showed numerous isolated and confluent clusters of gas bubbles,

corresponding in location to the entire right lobe of the liver, along with a small amount of free air beneath the right leaf of the diaphragm. Death ensued shortly after the roentgenologic examination. The roentgenographic findings were subsequently confirmed at autopsy.

Many investigators have demonstrated that gram-positive anaerobic spores are extensively distributed in nature and that they are relatively avirulent. They require an ideal environment to become pathogenic. The author presents this report of clostridial infection in the liver of a diabetic patient to demonstrate that gas gangrene may develop in the liver prior to death.—*W. M. McBride, M.D.*

POZNANSKI, ANDREW K. Cyst of the left triangular ligament of the liver. *Radiology*, Dec., 1959, *73*, 896–897. (Address: Henry Ford Hospital, Detroit 2, Mich.)

A study of the literature by the author revealed only 7 cases in which a cyst was located in one of the hepatic ligaments. In 4 of these 7 cases the cyst was located in the hepatic ligament, and in the other 3 cases in the ligamentum teres. These cysts may be classified as primary or secondary. Primary cysts may be of lymphangitic origin, or due to a developmental defect, or the result of peritoneal inclusion. The symptoms are variable, but a number of the patients have pain in the epigastric region, indigestion, or a full feeling more marked after meals. While the size of the cysts is variable, they are usually large and palpable. In a few of these cases roentgen examination of the gastrointestinal and renal systems was done, and in several instances an extrinsic pressure defect of the gastrointestinal tract was noted. Pathologically, the cyst in most cases was unilocular with a smooth endothelial lining and was filled with a clear or slightly cloudy serous fluid.

The author presents a brief review of the literature and reports 1 additional case in which the location of the cyst was in the triangular ligament of the liver. The cyst produced an indentation upon the stomach filled with barium and air. The indentation was shown by pneumoperitoneum to be a mass that was separate from the stomach and the diaphragm except for a fibrous attachment to the latter.

This cyst differed from the others which have been reported in its location and the fact that it contained hepatic tissue. None of the cysts were diagnosed prior to surgery.—*W. M. McBride, M.D.*

CAROLI, J., PORCHER, P., PEQUIGNOT, G., and DELATTRE, M. Contribution of cineradiography to study of the function of the human biliary tract. *Am. J. Digest. Dis.*, Aug., 1960, *5*, 677–696. (From: University of Paris and Saint Antoine Hospital, Paris, France.)

The authors studied by cineroentgenography the function of the common bile duct and the conditions of reflux into the duct of Wirsung. The cineroentgenograms were correlated with manometric studies carried out through an indwelling T-tube. Thirty-five per cent diodone was the contrast agent. The pressures were controlled and a synchronizer permitted determination of the pressure employed at the time of each roentgenogram.

The kinetics of contraction of the sphincter of Oddi were studied. The most frequent type of contraction was "antiperistaltic" in which the contraction wave moved from the ostium to the common duct. The opening of the sphincter was the reverse of this process, the widening starting at its superior point and progressing downward. In 1 of their patients the cineroentgenograms showed the mechanism of pseudocalculus formation in the lower common duct. Strong contraction of the sphincter caused the opaque medium to disappear completely. However, the pressure of the injection caused a dilatation of the distal common duct just above the sphincter. The lower border of the opaque medium was concave downward and simulated an ovoid filling defect.

The cineroentgenographic studies demonstrated that relaxing agents such as atropine sulfate changed the rhythm of contraction and relaxation, the sphincter remaining open for a longer period of time and closed for a shorter period. Morphine had an opposite effect.

The sphincter of Oddi was shown to be capable of autonomous muscular action, but its contraction could also be initiated when a duodenal wave reached the region of the ostium.

The cineroentgenographic studies demonstrated reflux into the duct of Wirsung in 30 per cent of the patients. When the anatomic features of the duct of Wirsung were normal, there was a higher incidence of reflux when the common duct pressure was increased or when the region of Oddi was relaxed by drugs or by a fatty meal. This was not true when the anatomic conditions were abnormal.—*J. L. Williams, M.D.*

GYNECOLOGY AND OBSTETRICS

BENNETT, ROBERT. Unequivocal radiological evidence of intra-uterine foetal death, including demonstration of gas formation within the foetal circulation: report of a case, and review of thirty-seven cases of foetal death. *Clinical Radiology*, July, 1960, *11*, 200–204. (From: King Edward Memorial Hospital for Women, Perth, Australia.)

Various signs of intrauterine fetal death which have been described include the following: (1) overriding of the skull bones with cephalic asymmetry (Horner, 1921; Spalding, 1922); (2) disproportion between fetal maturation and the estimated period of gestation; (3) absence of continued fetal growth with serial roentgenographic examinations; (4) absence of change in position of the fetus and particularly of its

extremities on serial roentgen examination; (5) formation of an angular kyphos in lumbar or dorsal spine; (6) collapse of thoracic cage; (7) roentgen evidence of gas in fetal circulation (Roberts, 1944); (8) the "halo sign," described by Deuel in 1947, due to increase in the width of the soft tissues between the radiolucent subcutaneous fat of the scalp and the bones of the fetal cranial vault; (9) disalignment of fetal skull bones at the coronal and lambdoid sutures prior to the tenth lunar month of pregnancy and in the absence of labor pains (Borell and Fernstrom, 1958). Such disalignment must occur before overlapping of the cranial bones is possible.

Gas in the fetal circulation appears early in comparison with other roentgen signs and may be seen within three days of the estimated time of death. Definite demonstration of such gas is an irrefutable sign of fetal death. If gas is present in sufficient quantity and in branching vessels and is unobscured by confusing shadows (such as maternal bowel gas, radiolucent fat layer of maternal psoas muscle, well-developed fetal subcutaneous fat layer around the extremities), it may at once be recognized by its bizarre appearance like gas in the biliary tree. This appearance is produced by gas in the portal vessels. Gas in umbilical vessels also will produce a characteristic shadow, sometimes with a round "end-on" appearance of the coiled vessels. Gas in the fetal heart can readily be identified by its position in the fetal thorax and its roughly triangular shape with the base caudad. The main dorsal vascular trunks produce characteristic parallel-walled and fairly wide gas streaks following the curve of the fetal spine.

A case is reported in which evidence of fetal intravascular gas and Deuel's halo sign were present, permitting unequivocal roentgenologic confirmation of fetal death. A review of roentgenograms of 36 patients who underwent prepartum roentgenographic examination showed evidence of fetal intravascular gas formation in 5. This review showed that Spalding's sign (overlapping of cranial bones) and evidence of lack of fetal tone were the most consistently helpful roentgen signs in arriving at a diagnosis of fetal death.—*Samuel G. Henderson, M.D.*

Genitourinary System

Béraud, Cl., Deffrenne, P., and Bressieux, R. Intérêt de la tomographie dans l'urographie du nourrisson et de l'enfant. (The value of laminagraphy in urographic studies of infants and children.) *J. de radiol., d'électrol. et de méd. nucléaire*, May, 1960, *41*, 230–235. (From: Clinique médicale infantile et Service de Radiologie, Hôpital Debrousse, 35 Chemin Saint-Irénée, Lyon-5^e^, France.)

Laminagraphy performed during urographic procedures may give important information which could not be obtained by other methods.

Many difficulties are encountered during urography in infants. For introduction of the iodine medium, venous injection by epicranial or jugular puncture is recommended and has been used in all the cases of the authors. A dose of 4 to 10 cc. of a 25 per cent tri-iodinated solution was found to be practical. Subcutaneous or intramuscular injection with hyalorunidase is painful, favors air-swallowing and is to be avoided. The presence of gas in infants, particularly in those with infection, is an objection to the use of abdominal compression. The administration of an antihistaminic drug is valuable for its quieting effect. Compression is not used to minimize agitation and this is compensated for by employing a cephalad Trendelenburg position which helps to keep the opaque medium more dense in the pyelocalyceal cavities.

As regards the laminagraphic technique, the indication for it depends on what is being looked for and what has been revealed in the earlier urographic roentgenograms. Its use is preferred in cases of abdominal distention in infants. The method consists of obtaining an early excretory roentgenogram taken after three minutes with fixed grid and high kilovoltage at 2/100 second. Then laminagrams are taken, more to evaluate the anatomic status than to study the renal function. Late laminagrams made in cases of renal anomalies are valuable for study of the ureters and bladder. The depth for useful laminagrams is from 3 to 5 cm. from the dorsal plane. The constant factors for a manual laminagram of an eight month old infant are 0.3 sec., 64 kv. and 100 ma. Automatic laminagraphy has been done at 1.0 second and with a 38° angle. In older and more cooperative children, an angle of 45° is preferred. To reduce radiation hazards, when standard urography is sufficient, routine laminagraphy should be omitted; however, in infants the expected results justify the systematic use of laminagraphy.

Among the great advantages of urolaminagraphy are the effacement of abdominal gases and the sharp delineation of renal contours. The spine may be studied for malformations and often the ureters can be seen in their full length, being located less than 1 or 2 cm. anterior to the renal plane. However, concretions of nephrocalcinosis are too fine to be visualized.

In conjunction with 281 urographic examinations performed in two years in their pediatric service, the authors made 52 excretory laminagrams, of which 31 were of children two years of age and 21 of children ranging in age from two to ten years. Laminagraphy was of decisive help in 3 children over two years of age, and in 12 children less than two years old.

If laminagraphy is to be systematically used in infants, the authors recommend it in children affected with myxedema, renal infection or insufficiency or in those with a dilated colon. In cases of tumor of the left hypochondrium, urolaminagraphy will differentiate an enlarged spleen from a big kidney, thus

avoiding the need of a retropneumoperitoneum.—*H. P. Lévesque, M.D.*

Squire, Lucy Frank, and Schlegel, Jorgen U. Pyelography in renal disease with hypertension; correlation between pyelographic findings and differential renal function studies. *Radiology*, Dec., 1959, *73*, 849–864. (Address: L. F. Squire, Strong Memorial Hospital, Rochester 20, N. Y.)

Experience over the past thirty years has shown that certain cases of hypertension are related to renal disease and that this hypertension may be curable if recognized before the heightened pressure becomes fixed. Studies have shown that a relative renal ischemia of still viable parenchyma may be the cause of this type of hypertension and that, in some cases, removal or repair of the guilty kidney tissue may result in a cure.

The purpose of this paper is to alert the radiologist to the limitations of the role he can play in helping the clinician select the salvageable patient. Seventeen hypertensive patients in whom complete studies were done are reported, with special emphasis on the correlation of intravenous pyelograms with differential kidney function studies. In all but 1 of these patients, excretion of the opaque medium was of good density on both sides, in spite of striking unilateral or bilateral depression of function, showing that the intravenous pyelogram is not helpful in indicating a malfunctioning kidney in the absence of morphologic changes. Furthermore, additional pyelographic findings, blood chemistry, urine and conventional function studies were often found to be normal in patients with renal ischemia due to some type of arterial obstruction. Causes of this obstructive arterial disease include: aberrant arteries, renal artery aneurysm, obstruction due to embolus, thrombosis, plaques and intimal proliferation, renal infarct, constriction of arteries in scar tissue secondary to trauma, and pyelonephritis.

The authors feel that, where no known contraindication exists, aortography should be performed in hypertensive cases in addition to differential kidney function tests with catheters in both ureters and simultaneous measurement of inulin clearance (glomerular filtration rate), volume in cubic centimeters per minute, and P.A.H. (para-aminohippuric acid) clearance (renal flow). Such studies often indicate depression of function on one side in the salvageable patient when all other means of discovering unilateral renal disease have failed, or they may prove the presence of bilateral disease, which would preclude operative intervention on the kidneys. The functional state of the good kidney may also be established by these studies.—*Donald N. Dysart, M.D.*

Brown, J. J., Owen, K., Peart, W. S., Robertson, J. I. S., and Sutton, D. The diagnosis and treatment of renal-artery stenosis. *Brit. M. J.*, July 30, 1960, *2*, 327–338. (From: St. Mary's Hospital, London, England.)

This paper constitutes a complete and thorough discussion of the problem of renal artery stenosis and is based upon the study of 22 patients. The disease is discussed with reference to clinical features, etiology, incidence, family history, pathology, diagnostic techniques, treatment and results. The roentgenologic aspect is covered in a discussion of the plain roentgenographic, intravenous pyelographic and retrograde aortographic findings.

The most common cause of renal artery stenosis is the atheromatous plaque. The ages in the present series ranged from seventeen to sixty-five years, the largest number being in the older group. A large percentage of the patients was found to have concurrent evidence of disease elsewhere, *i.e.*, intermittent claudication, ischemic heart disease, stroke, etc. A positive family history was only occasional. Physical examination and laboratory work may reveal hypertension, abdominal bruit, hypertensive retinal changes, polyuria, hypokalemia, proteinuria, and increased leukocyte excretion rate.

Special investigations in this disease include independent ureteric catheterizations and urinalysis for volume, sodium concentration, chloride concentration, inulin, creatinine and P.A.H. clearances and concentrations. In renal artery stenosis, output is decreased, concentration of sodium and chloride is decreased, clearance of inulin, creatinine and P.A.H. is inhibited and urinary concentrations of these substances are increased.

In many cases of renal artery stenosis, the kidney is noted on the plain roentgenogram to be smaller than the opposite. Intravenous pyelography is helpful in that the affected kidney, because of its increased concentration of inulin, concentrates the contrast medium better than the normal kidney. As a result, the affected kidney shows better contrast on an intravenous pyelogram than does the normal kidney. In cases of severe damage, however, this no longer holds true and poor function will be evident.

Selective retrograde aortography, using a variation of Ödman's technique, was used to investigate the size of the renal arteries. Using this method, 5 cc. of hypaque or urografin was injected directly into the renal artery. On occasion, injection of the contrast medium into the aorta was also done, on withdrawal. It was noted that the tip of the catheter caused stress phenomena which often had the appearance of stenosis.

Surgical correction should be undertaken only after intra-arterial pressures are taken to determine a pressure-drop across the stenosis.

Corrections should be limited to reconstruction if possible, and nephrectomy should be performed only if necessary. No operative deaths were encountered and 5 out of 6 operated patients experienced marked

resolution of their hypertensive disease. Pathologic studies of the affected kidneys showed tubular damage to be the most constant finding.

The details of all cases are tabularized.—*W. C. MacCarty, Jr., M.D.*

ZHEUTLIN, NORMAN, HUGHES, DIXON, and O'LOUGHLIN, BERNARD J. Radiographic findings in renal vein thrombosis. *Radiology*, Dec., 1959, *73*, 884–890. (Address: N. Zheutlin, University of California Medical Center, Los Angeles 24, Calif.)

The clinical syndrome of renal vein thrombosis occurs most frequently in children, over 50 per cent of the patients being less than five years of age. Ileocolitis is considered to be the chief predisposing cause in the young. In adults the condition may be secondary to thrombosis of the inferior vena cava with extension into the renal veins. Malignant growths of the kidney produce occlusion by direct invasion or by extrinsic pressure. In some reported cases, primary renal disease such as amyloidosis, glomerulonephritis, and malignant hypertension has produced thrombosis of the renal vein. There are few clinical cases in which a definite diagnosis is made. Although the roentgenographic findings reported to be associated with the syndrome are bizarre, they are not incompatible with the disease. It is possible to postulate different degrees of progression in vein thrombosis, producing gross changes in the kidney parenchyma and resulting in variable roentgenographic patterns. Thus, in acute thrombosis with massive infarction and perirenal hemorrhage, the intravenous pyelogram will show an enlarged nonfunctioning kidney. The retrograde pyelogram then shows the diffusion of the contrast agent into the kidney mass with an amorphous distribution of density. When one encounters a chronic, slowly progressive renal vein thrombosis, it is highly likely that adequate collateral circulation will take over the venous function, resulting in a relatively normal kidney. Between these two extremes lie the changes produced by renal edema. Here one may see the "polycystic" deformity and the incomplete and irregular pelvis.

Experimental surgical occlusion of the renal vein in dogs was performed in an attempt to reproduce renal changes. In acute occlusion, retrograde pyelograms made at hourly intervals showed increasing diffusion of the medium into the kidney. Attempts to produce renal changes on urograms in experiments simulating chronic venous occlusion were unsuccessful.

Three cases of renal vein thrombosis in man are briefly summarized. A urogram in one was interpreted as showing a polycystic kidney. In another, roentgenography was reported to show bilateral renal edema.—*Walter H. Jarvis, Jr., M.D.*

GONDOS, BELA. Rotation of the kidney around its transverse axis. *Radiology*, Jan., 1960, *74*, 19–25. (Address: 1720 Connecticut Ave., N. W., Washington, D. C.)

Rotation of the kidney about its transverse axis may be recognized on anteroposterior abdominal roentgenograms or urograms. The kidney is normally held in position by the fatty capsule, the renal fascia, the support of adjacent organs, intra-abdominal pressure, and the vascular pedicle. An increase in size of one or more of the adjacent organs, or a change in position, may cause encroachment upon the space available for the kidney, thus forcing the kidney to try to accommodate itself with a shorter diameter in the direction of encroachment. The vascular pedicle acts as a fulcrum and the lower pole is tilted anteriorly. This almost exclusive direction of rotation with the lower pole tilted anteriorly can be explained by the relative rigidity and solidity of the structures of the upper abdomen compared with the softer structures of the lower abdomen. The peritoneum has no significant role in rotation, and attempts to localize a mass as to its intra- or retroperitoneal position have been unsuccessful. In rotation around the transverse axis, the space-occupying agent acts on the vertical axis of the body, and it makes no difference whether the liver, gallbladder, spleen, or adrenal gland is the enlarged organ. There is no essential difference, with regard to the encroachment, whether the mass is adjacent to the upper or lower pole or is a tumor of the kidney itself.

Clinically, rotation around the transverse axis may be a useful sign in localization of abdominal masses as it is common with tumors of the kidney, or may be associated with displacement caused by the enlargement of adjacent organs. Recognition of rotation is important to avoid interpreting a blunted "lower pole" as a cyst or tumor, or to avoid incorrectly diagnosing a hypoplastic or contracted kidney. Rotation is also common with a ptosed kidney.—*J. C. Moore, M.D.*

SKELETAL SYSTEM

BROCHER, J. E. W. Konstitutionell bedingte Veränderungen des Wirbelbogens. (Constitutionally caused changes of the vertebral arches.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1960, *92*, 363–380. (Address: Place Claparède 5, Geneva, Switzerland.)

The various parts of the vertebrae arise from different groups of embryonic cells. Those cells which surround the chorda dorsalis ventrally form the chordal process. A dorsal group of cells grows in layers around the medullary tube and forms the neural processes via a cartilaginous phase. The latter may be recognized in a 12 mm. embryo (measured from head to sacrum). In the 70 mm. embryo, perichondral ossification of the vertebral arches takes place. The vertebral body is the only part of the

spine to develop via endochondral bone formation. The form and shape of the vertebral arches vary with the development of the neural tube. When the latter is experimentally removed, the vertebral arches develop hypoplastically. On examination of the entire spine, it is apparent that there is a proportional relationship between the form and size of the pedicles, the extent of the pars interarticularis, the posterior portion of the arch, and the articular process. These relationships vary with the spinal region as well as with the constitutional type of the individual. Pathologic changes which occur in the vertebral arches differ and sometimes are in sharp contrast to alterations in other osseous segments of the spinal column.

The greatest portion of the osseous-ligamentous border of the spinal canal consists of the vertebral arch. Only at the level of the atlas is the anterior border formed by the transverse ligament, whereas from C2 to L5 it is formed by the posterior wall of the vertebral body or the intervertebral disk, respectively. The lateral borders of the spinal canal are made up as follows: at the atlas, by the lateral masses; at C2 to C6, chiefly by the laminae; at C7 and D1, by the pedicle (one-third) and the laminae (two-thirds); at D2 to D12, mainly by the pedicle; at L1 to L4, one-half by the pedicle and laminae, each; at L5, one-third by the pedicle and two-thirds by the laminae. The posterior borders consist of the medial portion of the laminae.

The shape and size of the spinal canal vary at different levels of the spine. From C1 to C7, it is one-half the size of the corresponding arches; from D1 to D12 it is practically round; from L1 to L4, polygonal; and at L5, triangular. The transverse diameter in the lumbar area is 20–22 mm. and the anteroposterior diameter is 16–18 mm. The normal anteroposterior diameter at the atlas is 22–26 mm. (roentgenogram taken at 150 cm. distance). A decrease of 10 mm. or more suggests spinal cord compression. This measurement is also decreased in atlanto-axial subluxation due to congenital weakness of the transverse or other ligaments. Displacement of the odontoid process may be explained by similar factors. Such congenital abnormalities have not been recorded at any other level from C2 to L5.

The anterior portions of the arch, the pedicles, are particularly important, for example, in the measurement of the interpedicular spaces in spinal cord tumors. Congenitally short pedicles are typically found in chondrodystrophy (achondroplasia). An analogous situation in the rare entity of chondroectodermal dysplasia is described by Caffey. The so-called "extremity dwarf" presents a variety of vertebral malformations: small vertebral body, short pedicles, decrease in interpedicular distance, and a narrow foramen magnum. In the lumbar area, a decrease in the size of the pedicle produces sciatic pain. Butterfly- and hemivertebrae are associated with thick and wide pedicles, examples of the contrasting responses in various parts of the spine. In other words, these anomalies present hyperplasia in one site and hypoplasia in another.

The middle portion, pars interarticularis or isthmus, offers the most frequent examples of congenital defects. The isthmus normally is short, so the axes of the intervertebral joints lie in the same plane. In spondylolisthesis, besides the usual defect, there is lengthening and angulation of the pars interarticularis. It is also lengthened in pseudospondylolysis. These defects are probably due to abnormal resorptive changes on a congenital or constitutional basis. Less common are narrowing, thickening, or sclerosis of the isthmus. Spondylolisthesis may be associated with hypoplasia as well as with abnormality of form and position of the articular process.

The posterior border of the spinal canal consists of the laminae. At birth, the entire vertebral column is open posteriorly. Closure takes place from C3 to C5 at the end of the first year; at C2 at the end of the second year; and at C1 at the end of the fourth year. A physiologic spina bifida is seen in 33 per cent until the seventh year. The most frequent sites for spina bifida are at transitional levels of the spinal column, especially in the lumbosacral region where the incidence is 100 per cent at birth, 81 per cent in the fifth year, 44 per cent in the fifteenth year, and 10 per cent in adults. Spina bifida of the atlas is found in 3 per cent of adults and is best demonstrated by laminagraphic study. Spina bifida may often be associated with a myelocystocele, myelomeningocele, or a meningocele. However, not every patient with a spina bifida and neurologic complaints has one or another of the mentioned anomalies of the spinal canal. A rare defect of the laminae of L5, just posterior to the isthmus, is called a "retroisthmic cleft" and is usually accompanied by a spondylolisthesis of the contralateral side. In cleidocranial dysostosis, spina bifida with wide gaps or delayed closure is common. Hadley described a case of spina bifida of the entire spine in a six month fetus due to failure of the neural process to surround the notochord. This condition is incompatible with life.

Posterior "blocked vertebrae" involve the laminae and spinous process, rarely the intervertebral joint, and never the pedicle. The congenital anomaly differs from the acquired type (postinfectious or posttraumatic), since the latter only involves the body and is usually confined to two adjacent vertebral bodies. Hadley states that a round intervertebral foramen is characteristic of congenitally "blocked vertebrae," whereas it is concha-shaped in the acquired condition.—*J. Zausner, M.D.*

KOLÁŘ, J., and VRABEC, R. Röntgenologische Knochenbefunde nach der Hochstromverletzung. (Roentgenologic findings in bones after injury by a high tension electric current.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1960, *92*, 385–394.

(Address: J. Kolář, Radiologische Klinik der Karls-Universität, U nemocnice 2, Praha 2, Tschechoslowakei.)

Routine skeletal surveys and interval examinations will often disclose unsuspected lesions in patients who have been injured by a high tension electric current passing through their bodies. Changes occur at some distance from the actual path of the current as well as at the site of contact. Careful examination is required to detect hairline interruptions of the cortex or minor changes within the osseous architecture. Even these slight changes may not occur until several weeks after the trauma. Jellinek believes that the electric current acts as a mechanical trauma. Jenny advances the theory that an electric splintering in the bone causes an increase in intraosseous pressure due to evaporation of the fluid content of the bone.

The most frequent lesion is a linear or star-shaped fracture with a distinct or indistinct border. Cavitary lesions were found in 3 patients several years after the trauma. Bone necrosis usually has a good prognosis, although occasionally osteomyelitis and sequestration may follow. Periostitis is common and is probably due to infection or inflammation of the soft tissues. Subperiosteal hemorrhage produces changes similar to those in scurvy. Expansion of a phalanx resembling spina ventosa has also been observed. A six year old girl, who sustained an injury by a 220 volt charge, developed spontaneous sloughing of a distal phalanx, the fifth metacarpal and the distal third of the ulna. Neurotrophic changes similar to those in leprosy have been noted in the tips of the extremities.

In younger individuals a variety of developmental changes may occur. These include epiphyseal deformities, alteration of the metaphyses, hypoplasia, and occasionally hyperplasia. The latter may be due to hyperemia in cases of third or fourth degree burns or to the purulent complications. Joint involvement is also fairly common and may result in contractures, complete loss of mobility, subluxation, and, if infection supervenes, destruction of articular surfaces, ankylosis, and spontaneous amputation. Para-articular calcifications and ossifications have been observed. In 2 cases, after electrical injury osteochondritis dissecans occurred in the head of a metatarsal and metacarpal bone, respectively.

In general, healing progressed satisfactorily within several weeks, even with rather serious atrophy. Occasionally, several years elapsed before complete healing took place, particularly when the necrosis was rather severe. When infection of the soft tissues occurred, the prognosis was less favorable. Several cases required amputation because gangrene had set in.—*J. Zausner, M.D.*

General

Klatte, Eugene C., Campbell, John A., and Lurie, Paul R. Technical factors in selective cinecardioangiography. *Radiology*, Oct., 1959, *73*, 539–547. (Address: E. C. Klatte, 1100 W. Michigan St., Indianapolis, Ind.)

In obtaining over 300 cinecardioangiograms on 16 mm. film in the past two years, various technical details which may critically influence the diagnostic yield of this procedure have been evaluated. The unsharpness factor of the film image can be slightly reduced by using a 0.3 mm. instead of a 1.0 or 2.0 mm. focal spot; however, its use for cine-work is limited by the local heat capacity of the face of the anode. For this reason a 0.5 and 1.0 mm. focal spot combination on a high voltage tube appears most useful at present for cine-work.

Since the field size is a critical limitation in cineroentgenography, the image magnification factor is important. This is primarily a problem of engineering design since the magnification is decreased by increasing the target table-top distance and by decreasing the image tube front input phosphor distance. Also, since some spot roentgenogram devices remove the image tube front away from the patient, there is a distinct advantage in mounting the image tube on the table without interposition of a spot roentgenogram device. Image intensification itself can be used only to decrease radiation dose to a certain level, beyond which film detail suffers significantly. The focal length of the lenses will also alter the size of the film image, and with the limited field size available it is better to frame the entire image so that none of the picture will be cut off. Within these technical limitations one should strive for the fastest lens system possible to assure lower radiation doses.

The greatest and perhaps the only advantage of 35 mm. cineroentgenography is that the larger film frame allows better image detail because the reduction ratio of the original image is critically less than with 16 mm. film; however, cinecardioangiograms of comparable diagnostic yield can be readily produced on 16 mm. films with a significant decrease in radiation dose, cost, and handling problems.

The radiation dose to the patient depends upon many factors. In general, though, the diagnostic yield is much greater and the dose to the patient significantly less than with rapid cassette changers. With proper protection the radiation dose to the operator is less than 1.0 mr per examination. A high quality 16 mm. analyzing projector is necessary to appreciate fully the advantages of the cine-film method in cardioangiography. Also, high quality selective cinecardioangiography depends significantly on the proper catheter, contrast medium, injector, and positioning of the patient. Film with high contrast characteristics and fine grain size is more important in cinecardioroentgenography than high speed characteristics, and Eastman Kodak Linagraphy Shellburst film was found to produce the highest quality cinecardioangiograms. X-ray de-

veloper has been used in processing the film and a 200 foot strip has been successfuly processed in an Eastman Kodak X-Omat by attaching the end of the film to an x-ray film.—*Walter H. Jarvis, Jr., M.D.*

HODGES, PAUL C., and MOSELEY, ROBERT D., JR. Cinefluorography employing split-image television type image amplifiers. *Radiology*, Oct., 1959, *73*, 548–556. (Address: P. C. Hodges, 950 E. 59th St., Chicago, Ill.)

The authors describe in detail the roentgen-ray image amplifier recently developed by General Electric Co. This amplifier is a television type amplifier and differs from others in that it is directly sensitive to roentgen rays without the necessity of first converting them into visible light. The construction and operation are discussed and certain important differences between it and the amplifiers of Westinghouse, Philips, Morgan, and Moon are pointed out.

This General Electric image amplifier employs a tube which the manufacturer calls an X-icon. It is simpler than the tubes of Westinghouse and Philips and, unlike them, allows almost any desired amplification of image brilliance plus the advantage of multiple viewing tubes, including one for motion picture monitoring. It is vastly simpler than the Image Orthicon used in Morgan's amplifier and requires only simple and relatively inexpensive electronic circuits for the amplification of its signal.

The authors describe the installation of two of these X-icon image intensifiers in their angiographic laboratory. The installation is such that, with other attached equipment, a biplane split image television type amplifier cineroentgenographic system is produced, which permits the simultaneous display of both frontal and lateral images on each of the kinescope tubes from which the films are made. This equipment has been used for the most part only in experimental animals.—*Donald N. Dysart, M.D.*

KIRKPATRICK, JOHN A., and OLMSTED, RICHARD W. Cinefluorographic study of pharyngeal function related to speech. *Radiology*, Oct., 1959, *73*, 557–559. (Address: J. A. Kirkpatrick, St. Christopher's Hospital for Children, Lawrence and Huntingdon Sts., Philadelphia 33, Pa.)

Cinefluorography offers a technique for the visualization of the movements of the palate, tongue, and pharyngeal soft tissues during speech. The apparatus used in this study consists of a conventional fluoroscopic unit, an image intensifier of the electron optical type manufactured by the North American Philips Company, Inc., and a 16 mm. "sound on film" camera (Auricon Cine-Voice II). The camera has a 25 mm. f.95 lens focused at infinity. The fluoroscopic table is placed in the upright position, and the larynx is viewed in the lateral projection. A microphone is held 12 to 18 inches from the patient, and pictures are exposed at the rate of 24 frames per second as the patient speaks. A barium and water mixture is used to demonstrate regurgitation into the nasal cavity. The patient is exposed to a 5 inch circle of radiation for forty-five to sixty seconds, producing 30 to 35 feet of exposed film with 1,000 to 1,500 individual frames available for study.

There is a need for increased knowledge of the motor activities of the lips, tongue, mandible, soft palate, and pharyngeal soft tissues during speech in both the normal and abnormal subject. There are many unanswered questions in relation to muscle activity during speech. Cinefluorography with the synchronous recording of sound is being applied to the investigation of a variety of lesions of the pharynx. It aids in the selection of cases for surgery, and evaluation of different operative procedures. Cinefluorography also aids the prosthodontist by permitting visualization of the prosthesis during speech and evaluation of its functional adequacy. It should lead to more effective speech therapy. It was observed that, when velopharyngeal closure is anatomically impossible, the tongue tends to rise posteriorly (more than in a normal study) to raise the palate. Apparent anatomic apposition of the palate to the posterior pharynx may not connote functional closure, as shown by regurgitation of opaque liquid into the nasopharynx.

Cinefluorography and simultaneous recording of sound promise an elucidation of the relationship of physiology to speech.—*James C. Moore, M.D.*

MILLER, EARL R. Cinefluorography in practice. *Radiology*, Oct., 1959, *73*, 560–565. (Address: Department of Radiology, University of California Medical Center, San Francisco 22, Calif.)

This paper is addressed primarily to those contemplating the purchase of equipment for taking roentgen-ray movies. Its aim is to provide information regarding facilities required, the investment in time and money, information obtained with the technique, frequency of its use and its influence on the physician's practice. The cost of installation is usually the first consideration. The basic unit, which includes the ordinary fluoroscopic table with a spot filming device, phototimer, generator and overhead tube with tube stand, lists at approximately $20,000. An intensifying screen will add $6,500 to $12,000 depending on the size of the screen and the manufacturer. Installation of a high grade movie camera with automatic brightness control costs between $5,000 and $6,000. Less expensive units, in the range of $1,000, may be used however. Film processing equipment plus film splicer, viewer and projector bring the total cost to between $35,000 and $45,000.

Of importance in busy departments is the time involved in taking, processing, editing, viewing and

filing the films. Studying the movies alone usually takes an average of one hour per case. This factor in itself may limit the adoption of the technique. The use to which it will be put and the information expected must also be assessed. In its present state, cine-movies find their greatest use in research and teaching. Movies permit the study and restudy of certain functional body movements which are too rapid to be observed by conventional means. Studies of the pharynx in speech and in swallowing, the esophagus and cardioesophageal junction, the heart in angiocardiography, the urinary bladder, and the motion of joints practically constitute the field of usefulness of the cinefluorographic technique. Compared with its assets in teaching and research, the value of cinefluorography in service to patients is small. If a physician sees significant numbers of patients with esophageal, pharyngeal, bladder and joint dysfunction, then cinefluorography may be expected to provide valuable information. But for most private radiology practices it would be of little importance even if twice the existing number of such cases were available.

Finally, the financial yield from cinefluorographic services is extremely small compared with that from fluoroscopy and laminagraphy. A table is presented to show the relative incomes expected from the 3 techniques.

At the present time, therefore, roentgen-ray movies are of tremendous value in teaching and research and they have a small though definite place in the service of selected patients. The investment of funds, time and space, however, is inordinately great when compared to the income that can be derived from its use.—*Z. Petrany, M.D.*

FORMAN, MYRON, BORDEN, ANTHONY BOREADIS, and GERSHON-COHEN, J. Improvement of diagnostic value of photofluorographic films by electronic means; a preliminary report. *Radiology*, Nov., 1959, *73*, 774–775. (Address: M. Forman, Albert Einstein Medical Center, Northern Division, York and Tabor Roads, Philadelphia 41, Pa.)

Because of the difficulty of interpretation of photofluorographic roentgenograms, the use of a Philco Contrast Enhancer was investigated as a method of improving diagnostic quality. The Exicon is a closed television circuit which makes it possible to enlarge the roentgen-ray image and also to change shadings of contrast. The authors chose 70 patients at random for gastrointestinal examination both by conventional means and by photofluorographic technique. In a high percentage of cases an accurate diagnosis was made with photofluorographic methods as compared with regular roentgenograms. It is felt that this makes the method feasible for mass surveys and for teaching.—*James C. Moore, M.D.*

SCHWARZ, GERHART S. Kilovoltage and radiographic effect; investigation leading to a standard x-ray value scale (X.V.S.) system of simplified exposures for conventional and automatic radiography. *Radiology*, Nov., 1959, *73*, 749–761. (Address: 622 W. 168th St., New York 32, N. Y.)

For any proposed roentgenogram of a particular body part there is a certain optimum combination of exposure factors which will yield the best diagnostic quality. On either side of this optimum there is a variable range of exposures which will still result in roentgenograms of adequate diagnostic value. Exposure in photography depends on three prime factors: (a) the shutter speed expressed in seconds; (b) the lens opening expressed in F-stops and; (c) the brightness of the object, *i.e.*, the amount of light reflected by the object. Similarly, in roentgenography the exposure obtained will depend on :(a) timer setting in milliampere seconds; (b) kilovoltage; and (c) the thickness of the patient, which is an approximate expression of the amount of radiation which is transmitted through the subject to the film. In both techniques, the (c) factor is measured or estimated, and from this the (a) and (b) factors are determined either by rote, formula, or from a table.

In photography these determinations have been greatly simplified by the establishment of the so-called "E. V. S." system. This system consists of a set of simple index numbers assigned to each of the possible shutter settings and a similar set of numbers assigned to the lens opening settings. A given sum of any two settings labeled by this system will always give an identical exposure regardless of what the individual settings might be.

An identical system is not possible in roentgenography, however, because of the inconstant relationship of the kilovoltage to the roentgenographic effect. For this reason, the present investigation was carried out in order to determine the actual influence of kilovoltage upon the roentgenographic effect over a wide range of machine settings, and thereby to attempt to establish an exposure system similar to the E. V. S. system of photography.

A masonite bone phantom varying in thickness from 2 to 42 cm. was used. The criteria for a "correct" exposure were those which yielded optimum bone detail. Test exposures were made with varying kilovoltages (28 kv. peak to 133 kv. peak) to determine the exact doubling and halving points for each designated thickness. These readings were plotted on a graph and connected by curves. It was shown that no single exponent for the roentgenographic effect as a function of kilovoltage existed. However, the optimum exposures for each thickness were compared

and the doubling and halving kilovoltages for these exposures were plotted and used as standard points. When joined together, these points formed a "working axis" on either side of which was a range of settings which still yielded adequate exposures.

This zone is broad and covers more machine settings than occur under actual working conditions. It was possible, therefore, to develop a unit system using whole numbers to correspond to the necessary exposure factors as in the E. V. S. system. The caliper used by the technician for measuring patient thickness is labeled to read in roentgen-ray value (X. V.) units. After the body part is measured he sets the three machine controls (kv., ma. and timer) on such index figures that their sum equals the exposure value read off the unit caliper scale. This will effect an acceptable exposure regardless of the individual settings selected and no exposure table need be consulted. Such a caliper and unit system is presented here with tables to show the numerical labeling for the various kv. and mas. settings.

The system, now in actual use, has, in the author's opinion, resulted in a definite decrease in roentgenogram rejects and when error does occur the deviations tend to be small. The adoption of the unit system makes possible the future manufacture and design of much simpler machines with various degrees of automation. One could possibly eliminate kv. and ma. controls entirely and provide a single unalterable setting of these factors. The only variable would be that of the timer which could be set to read identically with the X. V. reading of the caliper. Further degrees of automation are also suggested and described. The final advantage of such a system is that it permits standardization of machine parts, films, and screens, eliminates unnecessary controls, limits error and makes possible partial or complete automation leading eventually to single knob control.—*Z. Petrany, M.D.*

REEVES, JOHN D. Progressive patient care in radiology. *Radiology*, Nov., 1959, *73*, 779–784. (Address: The J. Hillis Miller Health Center, University of Florida, Gainesville, Fla.)

Progressive patient care provides three zones within the hospital where care is tailored to the patient's needs. These three zones or areas are designated: (a) intensive care area for the seriously ill and for immediate postoperative care; (b) intermediate care area for those who need present-day nursing attention; (c) self help area for convalescents and others who may wish to take care of many of their own needs. Better patient care and easing of the economic burden should result.

This concept can be applied to the roentgenologic care of patients in the large hospital, but expert planning is necessary if the full medical and economic benefits of PPC are to be realized. To achieve the best patient care as well as economic operation, a department of radiology should be geographically located in the center of patient distribution. Clinical services most often in need of radiologic consultation, particularly orthopedic surgery and urology, should be located adjacent to radiology.

In planning hospital radiologic facilities, the following important statistical figures are accepted as standard guides: (1) 100 square feet of floor space per patient examined or treated per day, and (2) one roentgen-ray machine per 17 patients examined or treated per day. PPC applied to diagnostic radiology might result in four main radiology patient areas: (a) emergency radiology, (b) special procedures, (c) inpatient area, and (d) ambulatory areas. These four areas could be arranged as the four extremities of the letter "H". An arrangement such as this permits expansion in six directions.—*A. W. Sommer, M.D.*

RADIATION THERAPY

LATOURETTE, H. B., SIMONS, C. S., and LAMPE, I. A localization scheme for radiation therapy planning with the theratron. *Radiology*, Nov., 1959, *73*, 762–770. (Address: H. B. Latourette, University Hospitals, Iowa City, Iowa.)

The authors describe a system for lesion localization and beam direction utilizing preliminary anteroposterior and lateral radiographs incorporating "ruler" reference markers. The patient is usually placed in supine position on the treatment table, which is covered by a full length foam rubber pad 1 in. thick. All irradiation prescriptions consequently contain, as one of the coordinates of beam direction, the distance from the plane of the couch top to the central ray of the horizontal beam. A second coordinate is the distance, cephalad or caudad, from some prominent anatomic landmark. The third coordinate is the distance laterally from the midline.

A lateral radiograph is made using a cassette holder with opaque reference marks near its center. The patient is then removed from the table and a vertical ruler with opaque centimeter scale markings is placed in the exact center of the patient's former position. When these opaque reference marks on the two developed lateral films are superimposed, the distance from the table top to the point of interest in the patient can be read directly from the "ruler" radiograph. A similar method is used for the anteroposterior film. If rotation therapy is to be used, the patient's contour is traced on paper by the wire solder method, and localization by "ruler" radiograph is then carried out as described.

The accuracy of the localization is verified at the first treatment session by obtaining radiographs with cobalt 60 gamma rays. A special head holder used

both for localization and for positioning during therapy is described.—*John S. Alexander, M.D.*

Emery, E. W., Lucas, B. G. B., and Williams, K. G. Technique of irradiation of conscious patients under increased oxygen pressure. *Lancet*, Jan. 30, 1960, *1*, 248–250. (From: University College Hospital, London, W.C.1, England.)

In order to take advantage of the well-known principle that radiosensitivity of the cell is enhanced by an increase in oxygen tension, a compression chamber was built. The transparent chamber allows visual and auditory contact with the patient and eliminates much of the apprehension present when the patient is treated in a metal chamber. Incorporated in the apparatus is a system of pressurization which will minimize ear and sinus pain, ventilation to prevent retention of water vapor and carbon dioxide, and a double walled cylinder to eliminate the risk of explosive decompression. Total time of one treatment is usually less than half an hour. The authors hope to develop the technique so that it can be used for treating conscious patients at pressures up to four atmospheres absolute.—*Roger D. Cornell, M.D.*

DeGinder, W. L., and Lovell, B. K. Accelerated palliative radiation therapy of bronchial carcinoma with 250-kv. roentgen rays. *Radiology*, Nov., 1959, *73*, 684–692. (Address: W. L. DeGinder, Austin Radiological Group, 2410 Rio Grande, Austin 5, Texas.)

The authors report the results of a study of accelerated palliative radiation therapy of bronchial carcinoma with 250 kv. roentgen rays. Since 1946, approximately 560 patients have received 230 kv. or 260 kv. palliative therapy for primary bronchial carcinoma in the Dallas and McKinney Veterans Administration Hospitals. After exclusion of patients with unconfirmed diagnosis, incomplete follow-up, and those treated only for distant metastases, 446 cases remained for study.

The total dose was based on the predicted moist desquamation threshold. The factors were 250 kv. peak, 2.5 mm. Cu half value layer, 50 cm. target skin distance. Two opposite portals of 9×12 cm. were used. In eight days elapsed time, 3,600 r was delivered to each area in 6 treatments of 400 r (in air) each, or treatment was extended over fourteen days, with 4,000 r to each skin area in 10 treatments of 260 r (in air) each. The exit skin dose without back scatter was estimated to be 20 per cent. The tumor doses ranged from 1,500 r to 3,200 r.

Survivals in this report are considered only in relation to the period of possible benefit from the palliative treatment, namely, that period beginning with the institution of treatment. With the accelerated palliative therapy, 21 per cent survived one year or more. Ninety-seven patients were able to resume work for some period of time after treatment. Only forty-eight patients treated by the accelerated method were unable to return to home care within a month from the start of treatment.

The importance of a close physician-patient relationship is stressed. Relief of anxiety and the creation of hope contribute to the patient's subjective improvement. The accelerated treatment and early discharge from the hospital are active factors in the improvement of patient morale and a reduction of complaints. It is therefore difficult to make an accurate subjective evaluation of palliative results, but accelerated therapy does result in satisfactory palliation without producing painful sequelae to skin, pleura, or lung.—*A. W. Sommer, M.D.*

Rubenfeld, Sidney, and Kaplan, Gustave. Treatment of bronchogenic cancer with conventional x-rays according to a specific time-dose pattern. *Radiology*, Nov., 1959, *73*, 671–678. (Address: S. Rubenfeld, 477 First Ave., New York 16, N. Y.)

Forty-three consecutive patients with histologically proved cancer of the lung were treated with conventional roentgen-ray therapy according to a uniform, abbreviated time-dose pattern. Treatments were given with roentgen-rays generated at 250 kv., Thoraeus II filter, half value layer 1.25 mm. Cu at 50 cm. distance. The size of the field varied from 10×10 to 10×15 cm. All lesions received a calculated tumor dose of 3,000 r in fourteen elapsed days. The skin doses ranged from 4,000 r to 4,800 r.

The ages of the patients ranged from thirty-nine to seventy-three years. All tumors were histologically proved. All but 2 of the patients had distant metastases detected clinically, roentgenologically or at thoracotomy. The symptoms were controlled in 72 per cent of the series. Objective improvement was noted in 43 per cent of the patients. The most common symptoms to be alleviated were as follows: hemoptysis, 15 cases; pain, 14 cases; cough, 10 cases; dyspnea, 5 cases; superior vena cava syndrome, 1 case. There was no need to interrupt treatments because of radiation sickness, tracheitis, esophagitis, or skin reaction.

The abbreviated time-dose pattern achieved satisfactory palliation, shortened the hospitalization period, and did not induce serious debilitation.—*A. W. Sommer, M.D.*

Lougheed, M. N., and Maguire, G. H. Irradiation pneumonitis in the treatment of carcinoma of the breast. *J. Canad. A. Radiologists*, Mar., 1960, *21*, 1–10. (From: Montreal General Hospital, Montreal, Quebec, Canada.)

In irradiating lesions of the chest wall, it is at times impossible to prevent irradiation of pulmonary tissue. This paper deals with the incidence, correlated factors, and morbidity of these pulmonary changes in the treatment of cancer of the breast.

In the years 1953 to 1957, 491 new cases of breast carcinoma were seen. Of these, 255 received radiation therapy as follows: primary quadrate treatment, 94; postoperative irradiation to node bearing areas, 91; and to metastatic areas, 70.

The quadrate radiation technique includes fields directed tangentially to the breast, chest wall, axilla, and anterior mediastinum. Bolus is used. This large area is treated to tissue tolerance with 250 kv. peak, half value layer 2–2.4 mm. Cu at 50 cm. focus skin distance. The time varies from ten to twelve weeks.

The postoperative irradiation includes an anteroposterior mediastinal field 9 cm.×18 cm., an anteroposterior supraclavicular field 8 cm.×16 cm., and an axillary field 19 cm.×10 cm. A combination of 250 kv. peak and Co^{60} teletherapy is used. Treatment time is six to seven weeks.

The diagnosis of radiation pneumonitis is based on such clincal features as low-grade fever, prostration, dyspnea on exertion, nonproductive cough, and tachycardia. The roentgenographic changes include a coarse reticular or patchy infiltration, contraction of the lung, tenting of the diaphragm, absence of pleural effusion, and correlation of irradiation with the distribution of the pulmonary pathology.

The clinical features usually occur about one to four weeks after treatment. The roentgen changes are observed seven to ten weeks after treatment.

In the quadrate therapy group, 61 per cent had roentgen changes attributable to radiation. The average dose to those with pulmonary changes was 6,500 to 7,000 r in ten to eleven weeks.

In the postoperative irradiation group, 37 per cent had changes attributable to radiation. The average dose was 6,500 r in seven weeks to the lung apex. The extent of lung changes in this group was considerably less than in the quadrate therapy group.

If there is a critical level below which pneumonitis does not occur, it is probably between 2,500 and 3,400 r in seven weeks.

Of the 59 cases including both groups only 5 showed partial resolution of the radiation changes.

The authors briefly discuss the pathology of the process and point out the nonspecific histologic lung changes.

The lung alterations are usually asymptomatic. Less than 4 per cent produce symptoms. ACTH and cortisone were used in treating this small group of patients. The authors claim prompt relief of symptoms in the mild cases. Success or failure, however, should not be based on the return to normal of the chest roentgenogram, although steroid therapy may reduce changes that have already developed.—*Gerald J. Kurlander, M.D.*

Gish, James R., Coates, E. O., DuSault, Lucille A., and Doub, Howard P. Pulmonary radiation reaction: a vital-capacity and time-dose study. *Radiology*, Nov., 1959, 73, 679–683. (Address: J. R. Gish, 317 Goodhue Building, Beaumont, Texas.)

The object of this paper is to report a study of the relationship of the time-dose aspect of radiation therapy to radiation induced fibrosis and of pulmonary vital capacity as an index of lung function in those patients with fibrosis. The study includes a group of cases with adequate roentgenologic and clinical follow-up in which the lungs received incident radiation during therapy to the mediastinum, lungs, and node-bearing areas of the chest wall. In those cases in which reactions appeared, vital capacity studies were made. The pulmonary radiation reactions were classified into four groups as follows: I, pleural reaction only; II, pneumonitis—soft fluffy lesion, usually clearing within six months; III, pneumonitis clearing in from six months to a year and leaving moderate linear fibrotic residue; IV, pneumonitis clearing in from six months to a year and leaving extensive fibrotic residue. Irradiation was administered by means of roentgen therapy with half value layer of 1 to 3 mm. Cu or by cobalt teletherapy. The maximal dose to the lung varied from 2,000 to 8,200 r in periods covering five to eighty-two days.

Measurements of the total and three second vital capacities were made prior to treatment and subsequently in 24 patients. Any reduction in vital capacity, which in most instances was present three months after the beginning of radiation therapy, was not large in any case. None of the patients studied in this way showed any clinical signs of impaired pulmonary function. Decreased vital capacity seemed to correlate better with presence of disease in the patient as shown by later metastasis than with reports of fibrosis on the roentgenogram.

Pleuropulmonary reactions occurred in 44 per cent of those patients receiving 250 kv. roentgen therapy but in only 20 per cent of those receiving cobalt 60 therapy, although in general the latter group received a higher tissue dose. Some degree of pleuropulmonary reaction was demonstrated in 18 of 42 patients whose lungs were exposed peripherally; however, out of 10 patients who were treated over the mediastinum and medial borders of the lungs, a reaction was observed in only 1. There were few instances of pleuropulmonary reaction in patients irradiated tangentially. The incidence of reaction was about twice as great for field sizes of 15×20 cm. or larger than for 10×15 cm. ports or smaller.

Time-dose data for the groups showing some permanent residual fibrosis (III and IV) and for the groups showing temporary reaction only (I and II) were plotted on log-log paper, and a line representing the incidence of fibrosis was drawn below those points

in the first group. The dose level of about 3,700 r in twenty-nine days seems fairly definite. No distinction in results could be made between 250 kv. and cobalt 60 therapy, although most of the points above the line indicating temporary reaction only are from the cobalt group. The incidence of pulmonary reaction as previously described, 44 per cent for roentgen therapy and 20 per cent for cobalt therapy, suggests that the time-dose line for roentgen therapy may be lower. In a review of the literature, time-dose values consistent with this lung tolerance line were reported when similar techniques were used; with other techniques there was fibrosis following widely scattered time-dose combinations.—*W. H. Jarvis, Jr., M.D.*

KOLÁŘ, J., and VRABEC, R. Ungewöhnliche Knochenschädenformen nach der Bestrahlung im Beckenbereich. (Unusual bone damages following radiation treatment to the pelvic region.) *Radiol. clin.*, Mar., 1960, *29*, 109–116. (Address: J. Kolář, Radiologische Klinik SFN 1, U nemocnice 2, Prague, Czechoslovakia.)

The authors describe unusual findings and localizations of radiation damage to the innominate bones and the sacrum following radiation therapy for various pathologic conditions in the pelvis, usually malignant ones. They emphasize that the precursor of spontaneous fractures is an area of diminished bone density, sometimes combined with sclerotic changes. This can be seen not only in the neck of the femur but also in the pubic, ischial and sacral bones. This is of practical importance, as such findings can be easily confused on roentgenography with other pathologic conditions, especially bone metastases. Furthermore, this damage appears in women as well as in men who have undergone pelvic irradiation.—*Eckart Schackow, M.D.*

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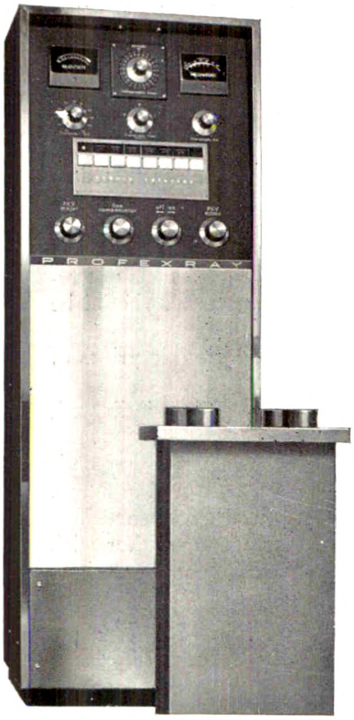

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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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COMPRESSION OF THE TRACHEOBRONCHIAL TREE BY THE ACTION OF THE VOLUNTARY RESPIRATORY MUSCULATURE IN NORMAL INDIVIDUALS AND IN PATIENTS WITH ASTHMA AND EMPHYSEMA*

By E. DEKKER, M.D.,† *and* R. C. LEDEBOER, M.D.‡
AMSTERDAM, HOLLAND

TALMA[26] in 1898 reported that asthmatic patients are often able to imitate at will the signs of an attack of asthma, when asked to do so. He also observed that normal persons were able to produce a wheezing expiration which seemed very similar to that which occurred during attacks of asthma. Since the wheezing sounds of asthma were similar in character over the entire thorax and changed simultaneously over the whole surface of the chest, he concluded that asthmatic wheezing had its origin in the trachea and larger bronchi, which were narrowed by a voluntary action. He quoted and confirmed the laryngoscopic observation of Van Hoek that in attacks of asthma the posterior wall of the trachea protruded into the lumen during expiration. Talma[26] thought that this narrowing of the larger airways was caused by a voluntary contraction of the smooth musculature.

In 1906 Strübing[22] confirmed that patients with asthma as well as normal subjects could produce a voluntary wheezing expiration at will. He, however, gave a different explanation and suggested that the origin of the tracheobronchial narrowing during the wheezing expiration might be the passive compression of the larger airways by a high intrathoracic pressure which was due to an abnormal breathing pattern. The influence of intrathoracic pressure on tracheobronchial compression had already been lucidly discussed by Einthoven.[9] That patients with asthma are able to imitate their attacks when asked to do so has recently been re-emphasized.[8] Dekker and Groen[4,6] confirmed the earlier observation that normal individuals can also learn to produce an asthma-like wheezing expiration at will. In their work they followed the instructions of Strübing:[22] "The forced expiratory movements of the asthmatic can best be learned in the following way. After a short inspiration one

* This investigation was supported in part by the Organisation for Health Research T.N.O.
† Second Medical Service, Wilhelmina Gasthuis, Amsterdam, Holland.
‡ University Department of Roentgenology, Wilhelmina Gasthuis, Amsterdam, Holland.

gives a slight cough. The cough movement is not completed, however, but instead a strong pressing and prolonged expiration is substituted. If one wishes to imitate the asthmatic breathing these respiratory movements are continued alternating with short inspiratory movements." By this method 16 out of 18 consecutive normal volunteers learned to wheeze at will within a few minutes.[4]

The mechanism of this "voluntary wheezing expiration" was studied for the following reasons: It can easily be produced at will both by asthmatic patients and by normal individuals which makes it suitable for an experimental approach. It was expected that study of the mechanism of voluntary wheezing expiration might throw some light on the pathophysiology of asthma and emphysema and on the problem as to whether the expiratory narrowing of the tracheobronchial tree during cough and in asthma and emphysema[4] is active[18–20] or passive[2,10,13,14,21,23,24,30] in nature.

In this paper roentgenologic studies and measurements are presented of the diameters of the trachea and main bronchi during voluntary wheezing in normal individuals and in patients with asthma and emphysema, supplemented by some observations during spontaneous and induced attacks of asthma.

METHOD AND MATERIAL

In order to avoid an influence of the contrast medium on the dynamics of air flow in the bronchi and on the reflex behavior of its walls,[10,24] the roentgen studies were done without contrast filling of the trachea and main bronchi.

Short time exposures were made in four projections: lateral, posteroanterior and both oblique projections, during respiratory arrest and—as much as possible—in the middle of the expiratory movement during "voluntary wheezing expiration." In a few cases observations were made during attacks of asthma which were either spontaneous or induced by the inhalation of an aerosol of histamine or of an allergen extract.

In order to obtain well defined images of the moving objects, an exposure time of only 0.04 second was used in combination with high voltage (125 kv.) and high-speed intensifying screens.

Twenty patients were thus roentgenographed during voluntary wheezing expiration, 10 who were normal and 10 who had asthma and/or emphysema. Of the latter group, 4 were examined during severe attacks of asthmatic dyspnea, 2 spontaneous and 2 induced. Direct measurements were carried out of the diameter of the air column in the trachea and when possible in the main bronchi. The outlines were traced on transparent paper and reproduced photographically on a smaller scale.

RESULTS

ROENTGEN FINDINGS

The roentgen changes in the major airways during the voluntary wheezing expiration in normals can be described together with those observed in asthmatic patients during voluntary wheezing expiration, or during spontaneous or induced attacks of severe dyspnea, as no essential differences between these groups were found, although there was some individual variation in the degree of the changes. Figures 1–6 illustrate the findings.

1. The *trachea* was considerably *narrowed* on all roentgenograms during voluntary wheezing expiration as compared to its configuration during respiratory arrest. This was noted especially on the postero-anterior roentgenogram. Sometimes a double contour could be observed near the posterior tracheal wall which was interpreted as the shadow of the protruding membranous part of the wall. The cartilage-supported part of the tracheal wall was also compressed as could be concluded from the diminution in its sagittal diameter.

This narrowing during expiration often differed considerably along the course of the trachea, giving its outlines an irregular wave-like appearance. The compression could frequently be observed to continue along the lower cervical part of the trachea (Fig. 1, *A* and *B*; 3, *A* and *B*; and 4, *A* and

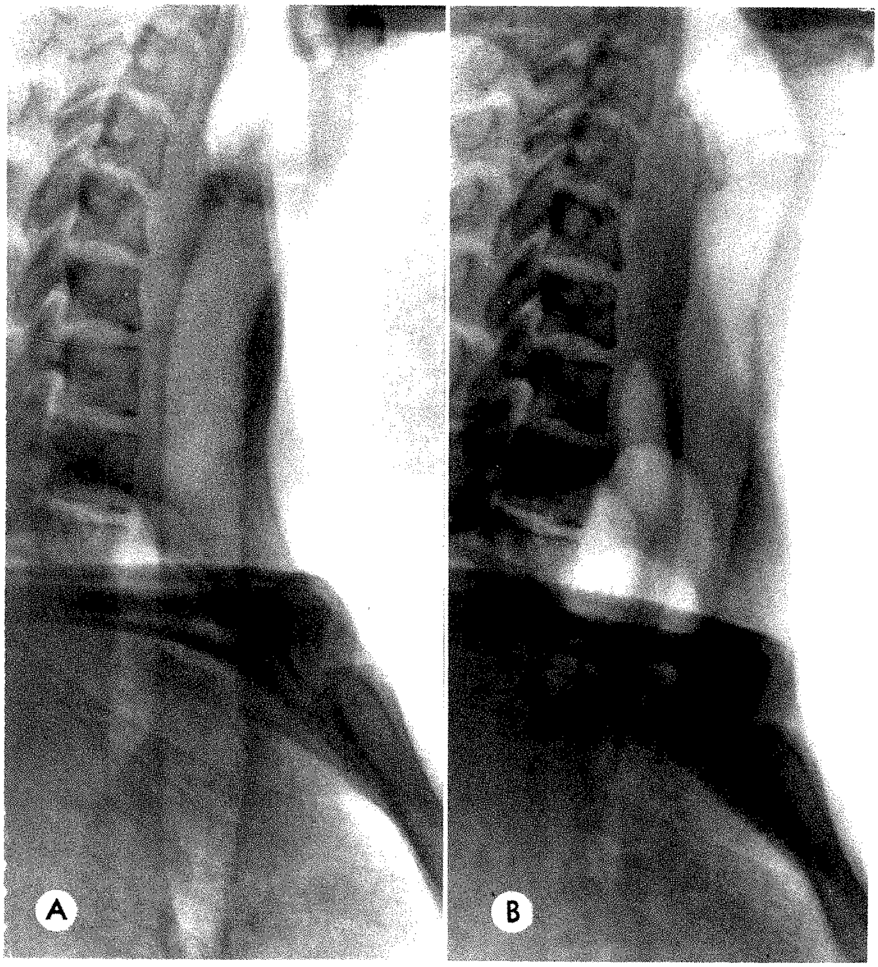

FIG. 1. (*A*) Roentgenogram of the trachea of a normal subject during respiratory arrest. (*B*) The cervical and intrathoracic parts of the trachea are narrowed and the cervical part is displaced in the ventral direction during "voluntary wheezing expiration."

B). There was a rather abrupt transition from the compressed lower to the wide open upper cervical part of the trachea, where the lumen retained its original size.

2. The *main bronchi* also appeared markedly narrowed during the wheezing expiration. In some of the subjects the lumina were reduced to a few millimeters (Fig. 2*B*). This narrowing of the major airways could easily be seen on fluoroscopy. It started very shortly after the beginning of the expiratory movement and continued almost throughout its entire duration.

In addition it was often possible to observe the dynamic behavior of the esophagus. In the right anterior oblique projection the wall of the esophagus and the posterior tracheal wall appeared as a common shadow, a few millimeters wide, which moved in a forward direction during the expiration.

3. The trachea became *shortened* during the wheezing expiration. The distance from the glottis to the bifurcation was reduced up to 5 cm. The bifurcation was driven upward and with it some other mediastinal structures were displaced. The aortic arch often shifted several centimeters craniad. The glottis and other laryngeal structures, on the other hand, descended. This shortening of the trachea was probably responsible for another phenomenon which could sometimes be observed: "ribbing" outline of the walls with clear demonstration of the

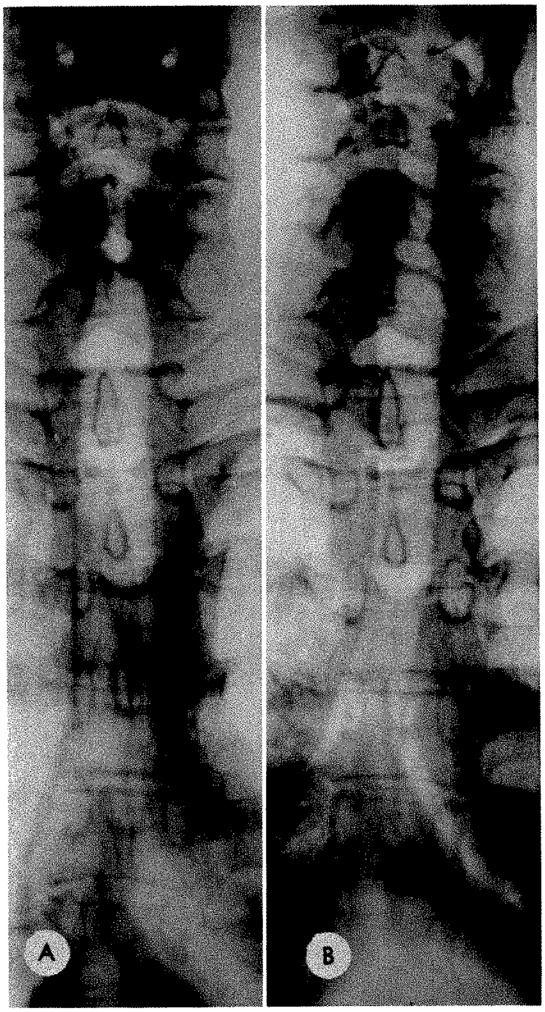

FIG. 2. (*A*) Anteroposterior roentgenogram of a normal subject during respiratory arrest. (*B*) During "voluntary wheezing expiration" the trachea and main bronchi are narrowed; the trachea is shortened and the glottis is open.

cartilaginous rings (Fig. 4, *A* and *B*).

4. During wheezing expiration the trachea altered its *position*. In the lower cervical part it was generally displaced forward (Fig. 1, *A* and *B* and 4, *A* and *B*). The shadow of the soft tissues of the lower neck was increased on the posteroanterior roentgenogram. The trachea also altered its course within the thorax, although its behavior here was much more variable (Fig. 7 and 8).

5. During wheezing expiration the *glottis* was wide open. This is clearly seen on the posteroanterior roentgenograms (Fig. 2, *A* and *B*).

6. The *pharynx* was widened in most of the subjects during voluntary wheezing expiration (Fig. 3, *A* and *B*; and 4, *A* and *B*). The hyoid bone was displaced caudally over about one cervical vertebra and so were the cartilages of the larynx.

7. On some roentgenograms the *larger intrapulmonary bronchi* near the hilus were visible. These also showed considerable narrowing during the wheezing expiration.

Figures 7 and 8 are line drawings illustrating the expiratory deformities during "voluntary wheezing expiration" in normal individuals and in patients with asthma and emphysema. Similar narrowings were demonstrated during episodes of dyspnea in these patients as illustrated by Figure 9.

QUANTITATIVE DATA

Tables I and II summarize some representative measurements of the tracheal lumen as seen on roentgenograms. Only those measurements are given which could be obtained with sufficient confidence in view of the comparatively weak contrast of the air column in the airways.

From these measurements it can be calculated that the frontal diameter of the tracheal lumen in normal individuals and in asthmatic patients was reduced from a mean value of 18.2 mm. to 13.4 mm. during voluntary wheezing expiration. The mean anteroposterior diameter was at the same time reduced from 19.1 to 12.5 mm.

Figure 10 is a schematic representation of a tracheal lumen at rest and in the narrowed state (natural size) based on these measurements.

DISCUSSION

During normal respiration the tracheobronchial tree changes its diameter: during inspiration the lumina are wide; during expiration they are narrowed. This has been described by a number of investigators.[10,12,15,16,24] These investigators were, however, mostly concerned with what might be called *static* changes in the diam-

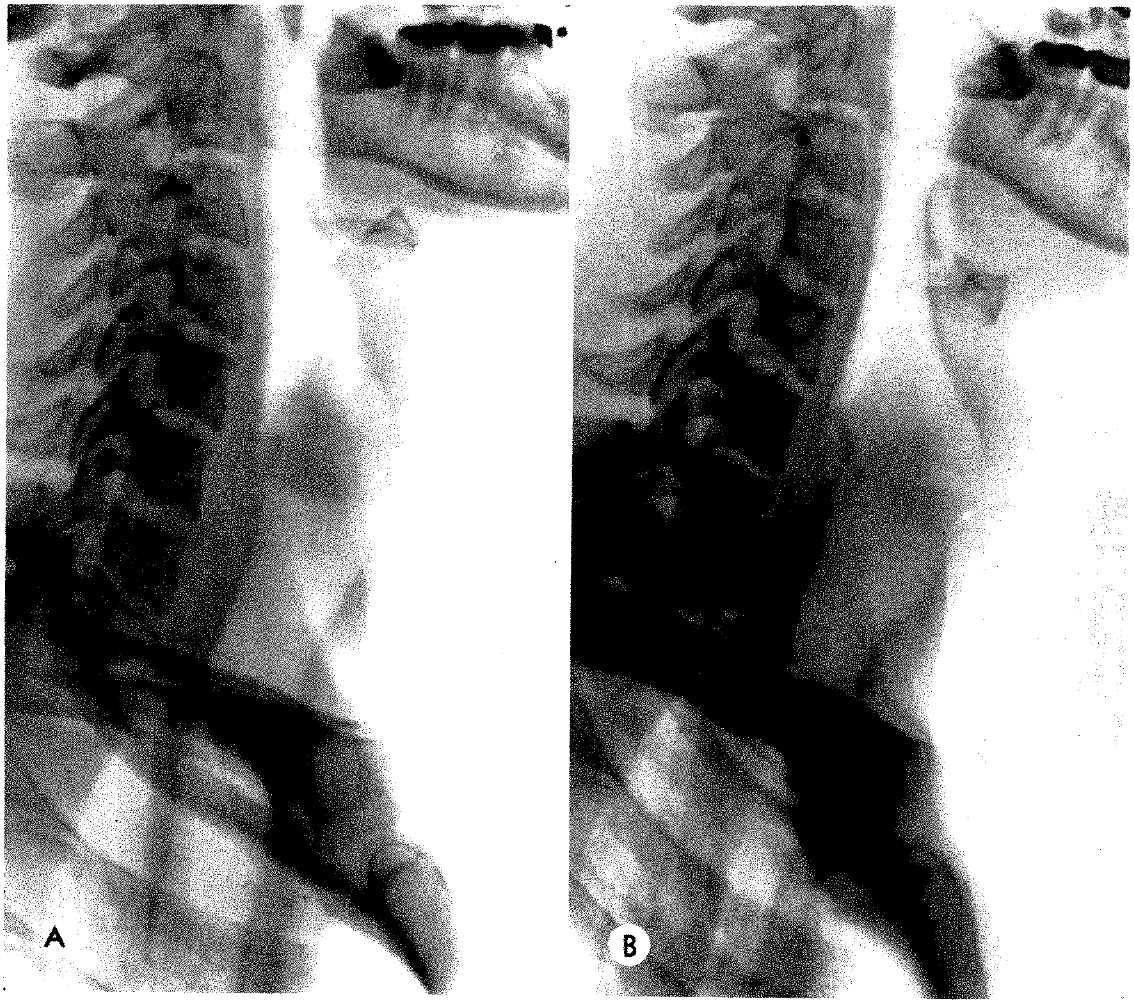

FIG. 3. (*A*) Roentgenogram of an asthmatic patient during respiratory arrest. (*B*) Narrowing of the cervical and intrathoracic part of the trachea occurs during "voluntary wheezing expiration."

eter of the bronchi. They based their studies on the comparison of roentgenograms taken during inspiratory and expiratory respiration *arrest*. Comparatively few studies have been performed on the *dynamic* changes in tracheobronchial diameter during physiologic or pathologic respiratory movements.

Dekker and Groen[4,6] have summarized some of the data from the bronchoscopic literature from which it can be concluded that under certain physiologic and pathologic conditions, *i.e.*, during attacks of asthma or in patients with emphysema and serious dyspnea, considerable narrowing of the trachea and cartilage-supported airways can be observed during expiration. The membranous part of the walls protrudes into the lumen giving it a triangular or crescent shape. There are also several roentgenologic observations of marked changes in diameter. Franklin and Janker[11] noted in the cat, during the expiratory phase of coughing, a reduction of the volume of the bronchi to about one seventh of normal size. Weltz[28] using kymography registered a difference of 18 mm. in the diameter of the trachea between inspiration and expiration in a patient during an attack of asthma. Stutz[23] and Weber[27] have also observed a difference in the diameter of the trachea during cough and during at-

TABLE I

MEASUREMENTS FROM ROENTGENOGRAMS OF AIRWAY LUMINA (IN mm.) IN NORMAL INDIVIDUALS AT REST AND DURING VOLUNTARY WHEEZING EXPIRATION

		H.P.	A.D.	M.F.	P.R.	F.M.	A.W.	J.M.	E.A.	E.D.	R.B.	Average	Per Cent
Sagittal diameter of trachea in upper thoracic aperture	at rest	26	26	25	26	25	29	27	—	30	24	26	
	wheezing	16	15	16	18	20	19	24	—	—	15	18	69
Frontal diameter of trachea at T2	at rest	22	21	20	20	20	24	20	22	24	—	21	
	wheezing	17	20	16	14	16	16	14	12	21	—	16	76
Left anterior oblique diameter of trachea 7 cm. below thyroid cartilage	at rest	24	19	20	23	—	26	23	20	19	—	22	
	wheezing	11	12	13	16	—	12	19	15	15	—	14	64
Frontal diameter of right main bronchus	at rest	20	—	—	17	19	19	14	—	—	—	18	
	wheezing	2	—	—	9	15	14	11	—	—	—	10	56
Frontal diameter of left main bronchus	at rest	12	14	—	14	14	14	14	—	—	—	14	
	wheezing	4	—	4	9	10	7	10	—	—	—	7	50
Length of trachea from glottis to bifurcation	at rest	180	—	—	165	—	180	160	—	—	—	171	
	wheezing	145	—	—	150	—	128	130	—	—	—	138	81

tacks of asthmatic dyspnea.[25] Dayman[3] found a momentary collapse of the thoracic trachea during cough in man. Similar observations were made by Ross *et al.*[21] and Holden and Ardran[14] by means of cineroentgenography during cough. These "dynamic" caliber changes of the tracheobronchial tree, apart from the difference in causative mechanism, vary considerably from the "static" caliber changes.[14,24]

The "static" changes are predominantly located in the smaller, more peripheral air-

TABLE II

MEASUREMENTS FROM ROENTGENOGRAMS OF AIRWAY LUMINA (IN mm.) IN ASTHMATIC PATIENTS AT REST AND DURING VOLUNTARY WHEEZING EXPIRATION

		L.P.	N.P.	A.B.	J.C.	J.D.	J.P.	K.S.	D.T.	C.D.	P.W.	Average	Per Cent
Saggital diameter of trachea in upper thoracic aperture	at rest	24	28	25	28	22	—	24	21	22	22	24	•
	wheezing	17	12	20	27	10	—	8	14	15	14	15	63
Frontal diameter of trachea at T2	at rest	23	23	18	29	18	24	23	17	20	21	22	
	wheezing	22	15	16	22	12	10	16	12	14	16	16	73
Left anterior oblique diameter of trachea 7 cm. below thyroid cartilage	at rest	24	24	22	23	18	23	25	18	22	24	22	
	wheezing	7	11	17	6	12	11	11	15	10	12	11	50
Frontal diameter of right main bronchus	at rest	—	—	—	—	12	16	16	—	15	—	15	
	wheezing	—	—	—	—	—	10	—	—	11	—	11	73
Frontal diameter of left main bronchus	at rest	—	—	—	—	11	11	15	—	13	—	13	
	wheezing	?4	—	—	—	2	11	14	—	10	—	9	69
Length of trachea from glottis to bifurcation	at rest	—	—	—	—	170	215	170	200	175	—	186	
	wheezing	—	—	—	—	—	215	170	180	155	—	180	97

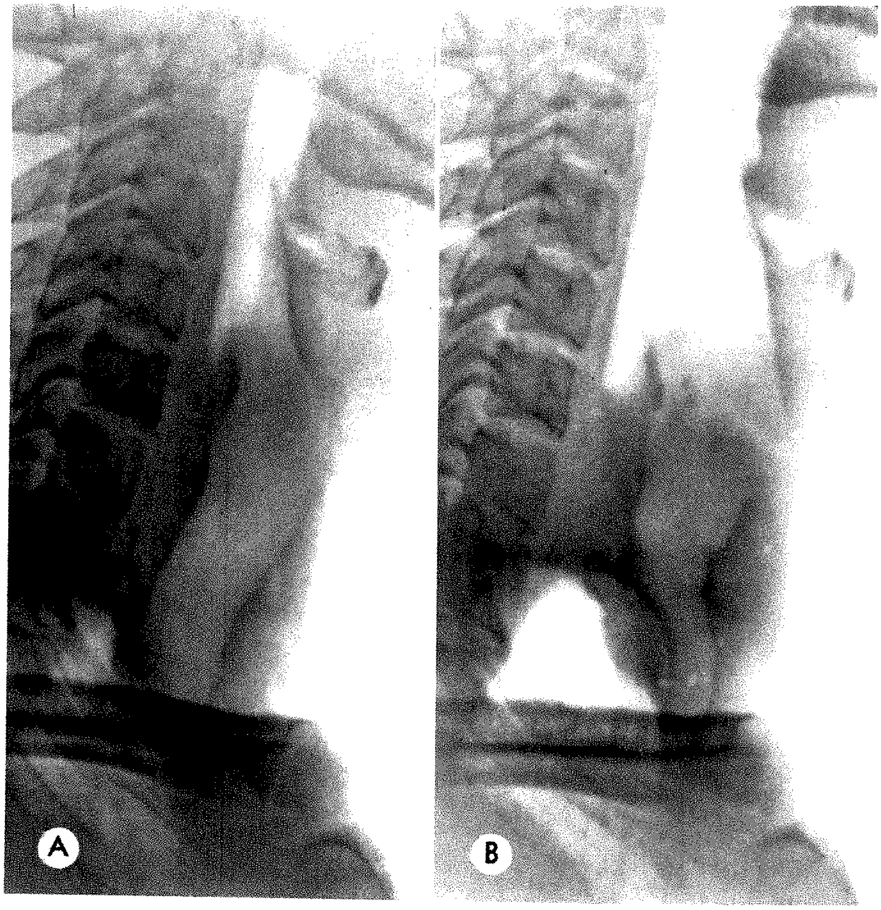

Fig. 4. (*A*) Roentgenogram of an asthmatic patient during respiratory arrest. (*B*) During "voluntary wheezing expiration" marked narrowing of the cervical part of the trachea occurs.

ways, whereas the "dynamic" changes appear to be located mainly in the more central airways.[18,24] The occurrence of strong dynamic respiratory caliber changes during cough and during attacks of dyspnea in patients with asthma and emphysema seems firmly established.

We have not been able, however, to find any studies on the influence of "voluntary wheezing expiration" on the diameter of the trachea and main bronchi in normal individuals and in patients with asthma. It seems that under these circumstances a similar considerable narrowing of the larger airways occurs. In other words, even normal individuals are able to produce a strong expiratory narrowing of the larger cartilage-supported airways without preceding closure of the glottis. These observations may contribute to several problems which are at present under discussion.

One of these problems has been the mechanism causing the "dynamic" caliber changes. Most authors[2,10,13,14,21,23,24,30] have accepted passive compression of the airways by high intrathoracic pressure as an explanation for the tracheobronchial narrowing. In coughing, for example, during the preceding phase of glottis closure, a high pressure of over 100 mm. Hg builds up in the thoracic cage.[21,29] Immediately after the explosive opening of the glottis, intraluminal pressure in the major airways is assumed to drop almost to zero whereas intrathoracic pressure is maintained for a short while, causing a great transmural pressure difference across the wall of the airways which are then externally compressed.

This view has been challenged by di Ri-

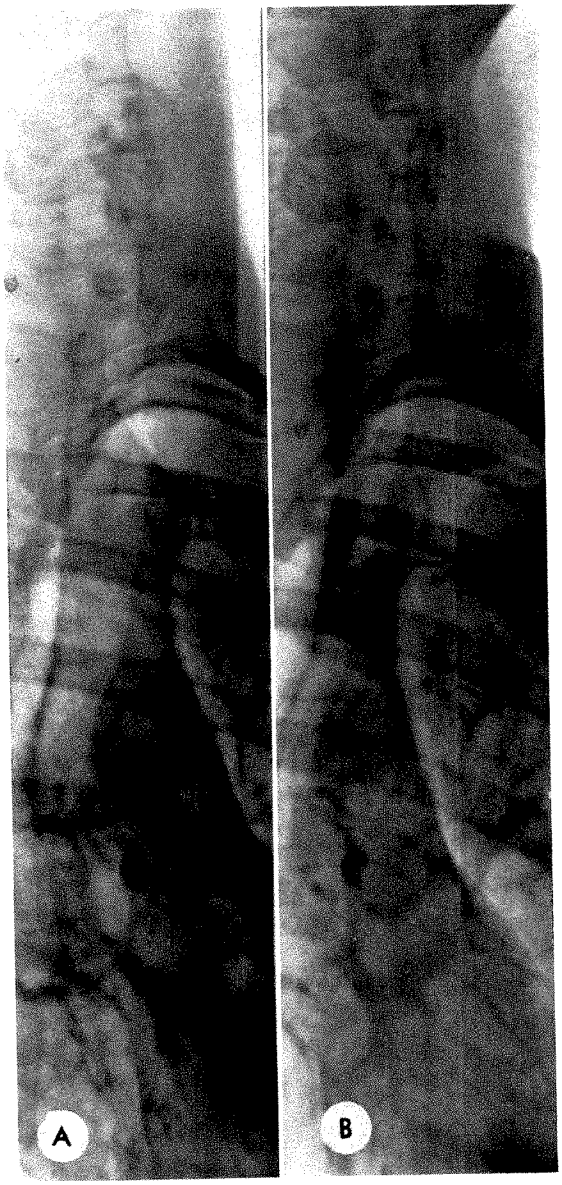

Fig. 5. (*A*) Trachea of an asthmatic patient in the right anterior oblique projection during respiratory arrest. (*B*) During "voluntary wheezing expiration" the intrathoracic part of the trachea is narrowed.

enzo[18-20] who ascribed the tracheobronchial dynamism during cough to an active reflex peristaltic movement of the muscular coats of the bronchial walls. Ross, Gramiak and Rahn[21] recorded intrapleural pressure and rate of air flow during a cough simultaneously by high speed cineroentgenography of the chest which permitted the visualization of the trachea. These investigators observed changes in the apparent diameter of the trachea which were synchronous with changes in intrapleural pressure once the glottis had opened. Although they obtained no evidence of a peristaltic movement along the bronchial tree, these authors prudently considered their evidence as insufficient to conclude that high intrapleural pressure is the only mechanism responsible for changes in tracheobronchial diameters during cough. They expressed the need for the investigation of an analogous situation not involving the cough reflex in order to obtain evidence that reflex bronchomotion is not responsible for the reduction in airway caliber. Our observations on voluntary wheezing expiration seem to give further support to their hypothesis of a passive compression.

The intrathoracic pressure during voluntary wheezing expiration was shown by Dekker, Defares and Heemstra[7] to rise to about 70 mm. Hg, a value which compares well with the results of Ross *et al.*,[21] obtained during coughing. Simultaneous direct measurement of endobronchial pressure by means of a special endobronchial catheter allowed an estimation of the transmural pressure which was compressing the airways at different levels[4] (Table III). It was shown *in vitro* during compression experiments on human tracheobronchial tissue obtained post mortem that such transmural pressures could considerably narrow the respective parts of the bronchial tree.[4]

It would seem at first sight that the narrowing of the trachea would cause a high airflow resistance. Our roentgenographic measurements provided a basis for a tentative calculation[1] of air flow resistance in the

Table III

Transmural Pressure, Compressing the Airways during Voluntary Wheezing Expiration[4]

	mm. Hg
Larger intrapulmonary bronchus	15
In or near mean bronchus	55
Upper intrathoracic part of trachea	68

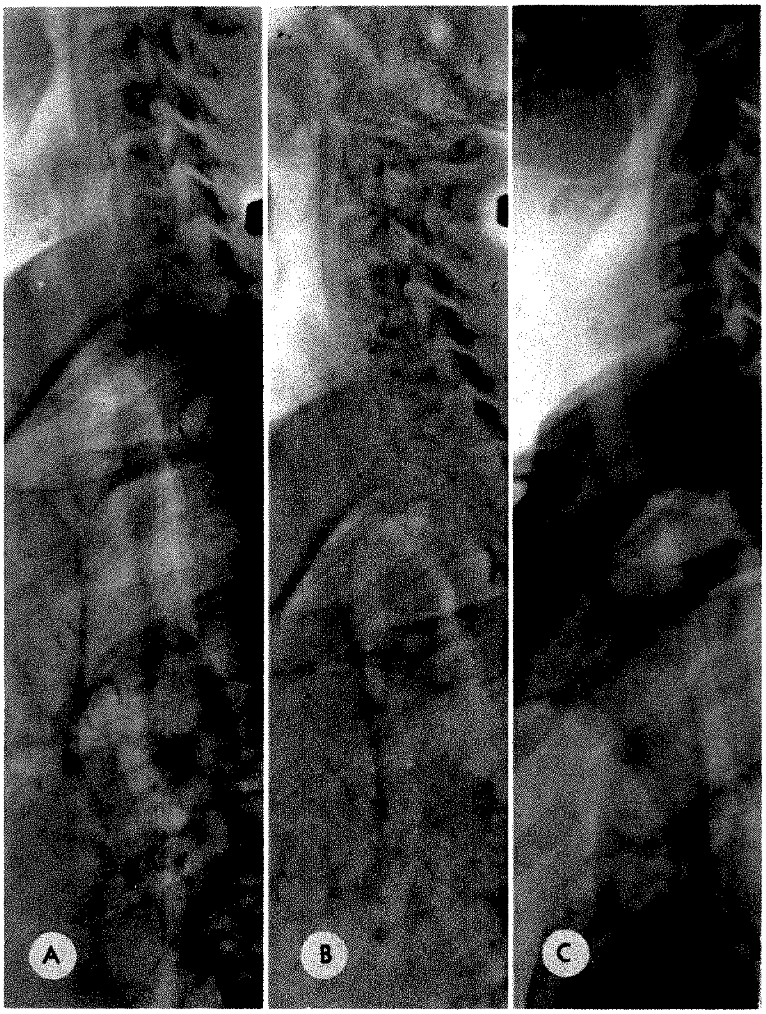

Fig. 6. (*A*) Trachea of an asthmatic patient in the left anterior oblique projection during respiratory arrest. (*B*) During "voluntary wheezing expiration" and (*C*) during a spontaneous attack, a narrowing of the trachea and main bronchi occurs.

trachea in its normal and in its compressed state. Table IV gives a summary of the results of such calculation based on the dimensions shown in Figure 10. From this calculation it can be seen that the air flow resistance of the normal trachea is almost negligible. The calculated air flow resistance of the narrowed trachea is also negligible at low air speeds and even in the compressed state its value remains comparatively low. Obviously, the caliber of the human trachea contains a wide margin of safety.[17,30] Tracheobronchial compression by high intrathoracic pressure may also play a role in the pathophysiology of attacks of dyspnea in patients with asthma and emphysema. In asthmatic patients primary narrowing of the smaller peripheral bronchi will tend to raise the intrathoracic pressure during expiration. High intrathoracic pressure will tend to cause further compression of the airways, thus initiating a vicious circle.[9] In this case high intrathoracic pressure can be considered to be a compensatory phenomenon. Since our results indicate that narrowing of the airways can also be brought about in asthmatic patients by a primary action of the voluntary respiratory musculature raising the intrathoracic pressure, the alternative possibility, that at least in some attacks of asthma a primarily disturbed breathing

TABLE IV

CALCULATED AIR FLOW RESISTANCE IN THE TRACHEA IN ITS NONCOMPRESSED AND COMPRESSED STATES

	Air flow velocity in l./sec.			
	0.25	0.5	1	2
Air flow resistance in cm. H_2O/l./sec.				
Noncompressed trachea	0.0082	0.0082	0.017	0.035
Compressed trachea	0.061	0.072	0.17	0.35

mechanism may narrow the airways, deserves further consideration. Although it has been possible to provoke and register reproducible psychogenic attacks of asthma in the laboratory,[3,6] hardly any research has been done on the nature of the pathways conveying the emotional influences from the central nervous system to the lungs. Among several mechanisms which might be involved in these phenomena, tracheobronchial compression of the airways caused by a primary disturbance of the action of the voluntary respiratory musculature deserves further consideration and study.

SUMMARY

1. Roentgenographic studies made during "voluntary wheezing expiration" revealed that normal individuals as well as patients with asthma and emphysema can voluntarily narrow their tracheobronchial tree to a considerable extent.

2. This narrowing was probably caused

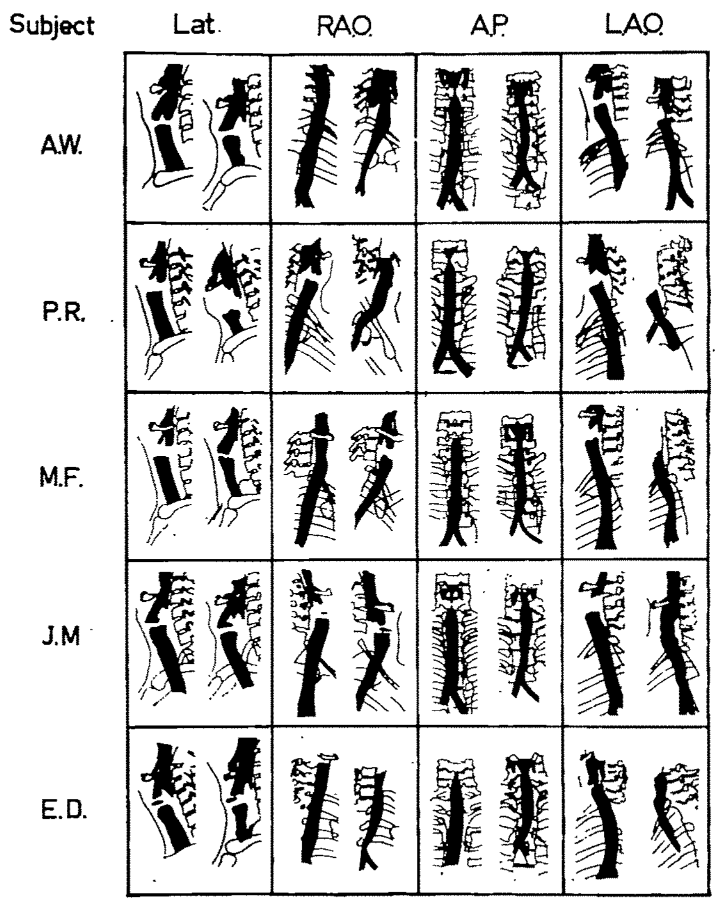

FIG. 7. Line drawings of the trachea and main bronchi of normal subjects in the lateral, right anterior oblique, anteroposterior and left anterior oblique projections during respiratory arrest (left) and during "voluntary wheezing expiration" (right).

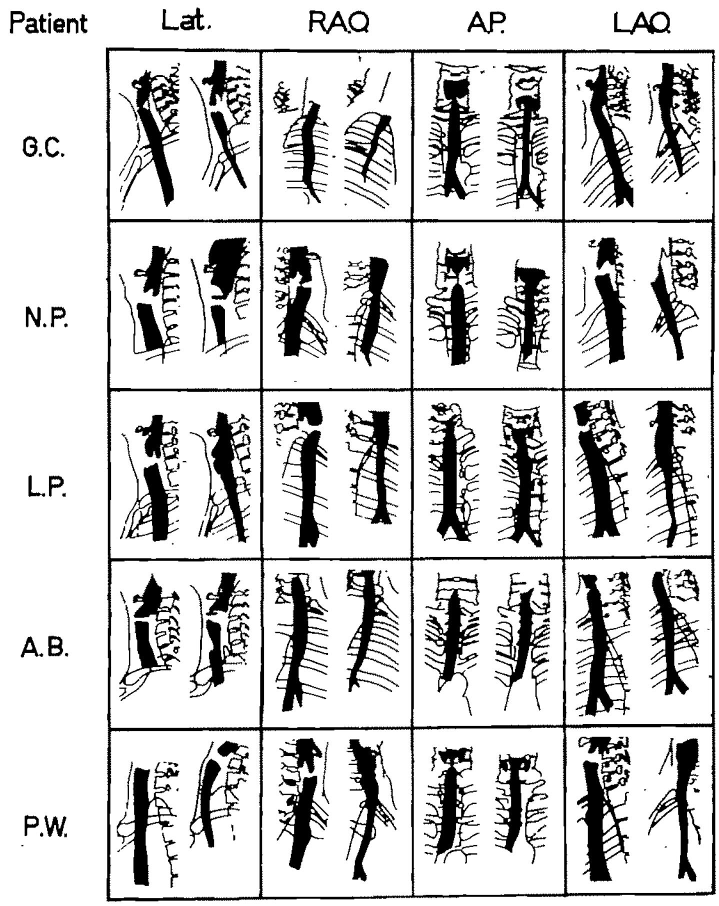

FIG. 8. Line drawings of the trachea and main bronchi of asthmatic patients in the lateral, right anterior oblique, anteroposterior and left anterior oblique projections during respiratory arrest (left) and during "voluntary wheezing expiration" (right).

by a high intrathoracic pressure which passively compressed the airways.

3. Calculations revealed that the air flow resistance was almost negligible in the normal trachea and remained low, even in its compressed state.

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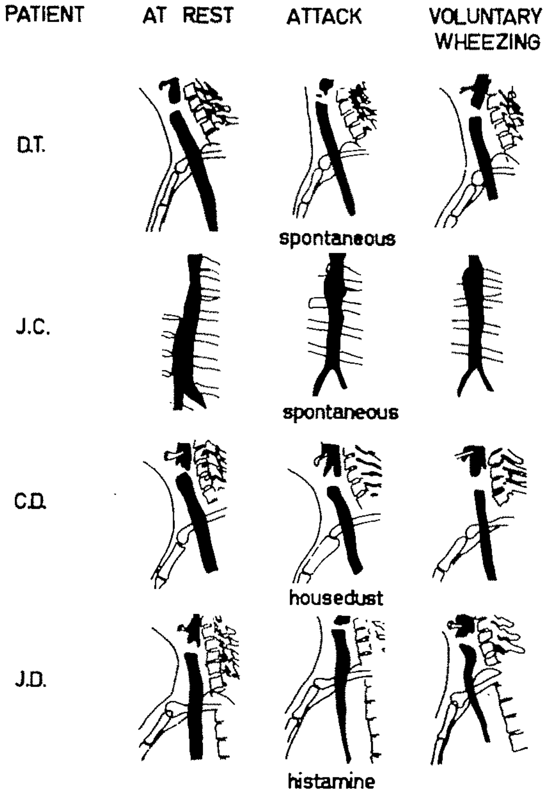

FIG. 9. Line drawings of narrowing of the trachea of asthmatic patients during asthmatic attacks (both spontaneous and induced) and during "voluntary wheezing expiration," as compared to at rest.

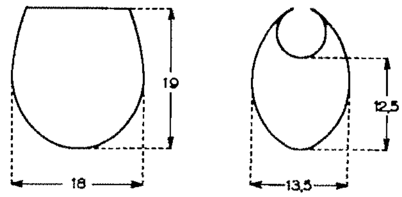

FIG. 10. Schematic representation of the trachea in its normal and compressed states, based on the means of the roentgen measurements at the second thoracic vertebra (natural size).

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ANGIOCARDIOGRAPHY IN BULLOUS EMPHYSEMA: ITS ROLE IN SELECTION OF THE CASE SUITABLE FOR SURGERY*

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SURGICAL treatment of bullous emphysema has become generally accepted as being beneficial in selected patients.[8,17–19,29] In this report, cases illustrating the role of angiocardiography in the diagnosis of bullous emphysema[18,28] and in the selection of the patient suitable for surgery are presented. Thereby, criteria for the use of angiocardiography for treatment of bullous emphysema are promulgated.

MATERIAL AND METHOD

Sixty adult patients, referred for angiocardiography in order to evaluate the type and degree of emphysema (generalized or bullous), form the basis of this study. The clinical, laboratory and roentgen features of each case were reviewed. Of these, 8 were selected for detailed presentation because they best serve to illustrate the role of angiocardiography in the selection of the patient with emphysema that can be benefited by surgery. Angiocardiography was done in the erect frontal position utilizing 14×17 inch film in order to include the whole of the lungs. The stereo shifter with grid cassettes permitted two roentgenograms per injection.[21] Opacification of the right heart structures, pulmonary artery and pulmonary arterial tree was secured on the first roentgenogram which was usually exposed three and one-half seconds after the beginning of injection. The other roentgenogram was exposed at seven and one-half seconds and provided a view of the opacified pulmonary veins, left atrium and ventricle. Serial studies at one second intervals were made in some instances. The contrast substance was urokon sodium (70 per cent) in 50 cc. doses. No severe reactions occurred.

REPORT OF CASES

CASE I. *Generalized and bullous emphysema; surgery contraindicated because of severe generalized emphysema.* A fifty-two year old male (N.Y.H. No. 365302) was admitted on April 3, 1955, because of a productive cough and progressive dyspnea of eight years' duration. During that time he had had four hospital admissions for acute bronchitis, bronchopneumonia and pneumonia. He also had had "double pneumonia" at the age of thirteen years. In the past two years he had developed polycythemia, cor pulmonale and congestive heart failure. Two weeks prior to admission there was increased cough, blood streaked sputum and right middle lobe pneumonia. On examination, the patient was acutely and chronically ill, orthopneic and gasping with wheezing respirations at the rate of 40 per minute. Cyanosis of the lips and nailbeds was marked. The chest was barrel-shaped, hyper-resonant and use of the accessory muscles of respiration was evident. The breath sounds were distant; coarse rhonchi and wheezes were heard in the upper parts of the chest with fine inspiratory and expiratory rales at the bases. The heart was not enlarged. The liver was 9 cm. below the right costal margin and the ankles were edematous.

The conventional roentgenogram of the chest (Fig. 1*A*) revealed a long thorax with markedly distended lungs. An angiocardiogram (Fig. 1*B*), made three years prior to admission, showed a large pulmonary artery and branches with meager and wiry pulmonary arterial circulation to the upper lobes which appeared to narrow abruptly in the mid-zone of the thorax ("the winter tree pattern"). The pulmonary arterial circulation to the lower lung fields was delayed and extended only a slight distance beyond the hilus. Two and a half seconds later (Fig. 1*C*)

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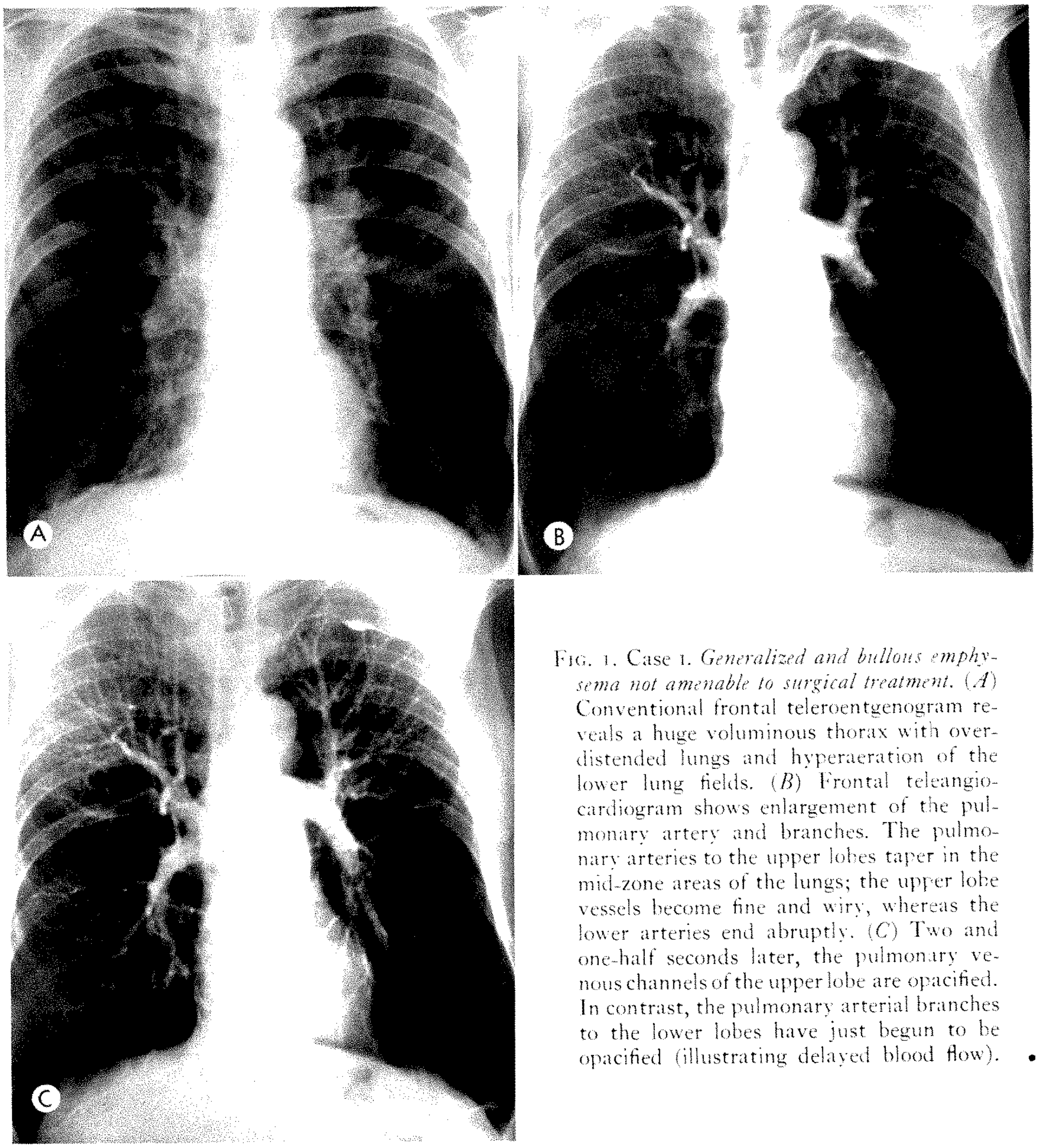


FIG. 1. Case 1. *Generalized and bullous emphysema not amenable to surgical treatment.* (*A*) Conventional frontal teleroentgenogram reveals a huge voluminous thorax with overdistended lungs and hyperaeration of the lower lung fields. (*B*) Frontal teleangiocardiogram shows enlargement of the pulmonary artery and branches. The pulmonary arteries to the upper lobes taper in the mid-zone areas of the lungs; the upper lobe vessels become fine and wiry, whereas the lower arteries end abruptly. (*C*) Two and one-half seconds later, the pulmonary venous channels of the upper lobe are opacified. In contrast, the pulmonary arterial branches to the lower lobes have just begun to be opacified (illustrating delayed blood flow).

there was pulmonary venous filling of the upper lobes, whereas the pulmonary circulation to the lower lobes had only reached the mid-zones of the lungs. Pulmonary function studies, four years prior to admission, had showed the vital capacity to be 3,600 cc. Three years later it had been only 1,400 cc.; prior to admission it was 2,100 cc.

The patient died seventeen days after entry (April 20, 1955) and at autopsy the lungs were tough, leathery, and of fibrous consistency, especially the lower lobes. Numerous small blebs were scattered over the entire surface of both lungs. Only small bullae of the lower lobes, measuring up to 5 cm. in diameter, were present. The cut surfaces of the lower lobes and the peripheral and apical portions of the upper lobes had a coarse spongy texture. There was moderate generalized emphysema and fibrous thickening of the alveolar walls. The bronchi were dilated and the elastic and muscular elements were largely replaced with fibrous tissue. There was marked fibrous thickening of the smaller arteries and the lumina of many were plugged

with organized thrombi. The diagnosis was bronchiectasis, generalized and bullous emphysema and pulmonary fibrosis. The heart showed the characteristic findings of cor pulmonale; the right ventricular wall measured 9 mm.

Comment. Clinically the patient had all the features of pulmonary emphysema. The conventional roentgenogram also showed cor pulmonale while the angiocardiogram showed the classic signs of generalized emphysema but without bullae. The serious and progressive character of the emphysema was also indicated by the pulmonary function studies.

CASE II. *Generalized and bullous emphysema also unsuitable for surgery.* A sixty-six year old butcher (N.Y.H. No. 431550) had had frequent upper respiratory infections. For five years there had been a chronic cough with thick, tenacious, stringy sputum. Dyspnea on exertion followed so that shaving or eating caused attacks. On examination the patient was thin, afebrile, and chronically ill. Slight cyanosis of the lips and nailbeds was present; the respirations were rapid and shallow. The chest was asymmetric with a markedly increased anteroposterior diameter. Percussion was hyper-resonant with almost absent breath sounds in the left chest. The pulse rate was 90 and the blood pressure 200/110 mm Hg. The conventional frontal roentgenogram of the chest (Fig. 2*A*) showed a voluminous thorax with flattening of the diaphragms. An angiocardiogram (Fig. 2*B*) showed moderate enlargement of the pulmonary artery and branches, while the pulmonary arterial tree ended abruptly in the mid-zones of the lungs. The vascular pattern was interpreted as being typical of generalized emphysema except for a single large bulla at the left base. Pulmonary function studies showed the vital capacity to be only 1,400 cc.

Comment. This case illustrates the characteristic angiocardiographic features of advanced generalized pulmonary emphysema.

CASE III. *Bilateral bullous emphysema; improved by right upper lobectomy.* A fifty-four year old man (N.Y.H. No. 643952) had had a fifteen

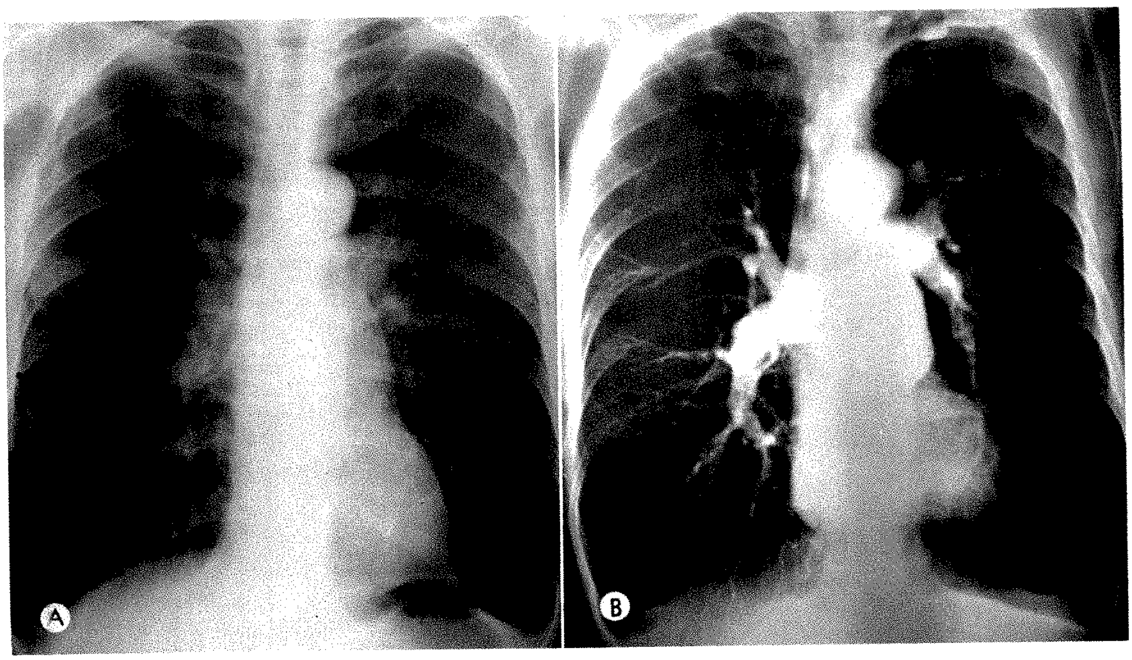


FIG. 2. Case II. *Generalized and bullous emphysema also unsuited for surgery.* (*A*) Conventional frontal roentgenogram reveals a voluminous thorax with increased translucency of the lungs, especially the bases. The pulmonary artery segment is prominent. (*B*) Frontal angiocardiogram shows enlargement of the pulmonary artery and branches. There is marked decrease in the pulmonary arterial tree, especially of the left lung. The right lung shows the wiry ("winter tree") pattern of generalized emphysema. The left lung shows the abrupt termination of the pulmonary arterial tree due to bullous emphysema.

year history of cough with profuse expectoration. Previously he had had pneumonia and bronchiectasis of the left lower lobe. For two years there had been increased dyspnea with drenching night sweats and loss of twenty pounds. He was able to climb only one flight of stairs. On examination the patient was thin, pale and chronically ill but there was no cyanosis or edema of the ankles. There was hyperresonance on percussion of the chest while the breath sounds were diminished, with wheezes over the entire thorax. The conventional frontal roentgenogram of the chest showed a voluminous thorax with increased radiolucency of the upper lung fields (Fig. 3*A*). An angiocardiogram (Fig. 3*B*) showed the pulmonary artery and branches to be moderately enlarged. The pulmonary vasculature of the upper lobes narrowed abruptly just beyond the hilus. The midzone pulmonary arterial branches were markedly decreased in number and caliber and were distorted, especially on the right side. The pulmonary vasculature of the lower lobes appeared displaced downward, more on the right than the left side, but were of normal caliber in the mid- and outer zones.

The arterial O_2 saturation was 90 per cent (predicted value 97 per cent). The pulmonary artery pressure was 31/14 mm. Hg at rest and 57/23 after exercise. The pulmonary vascular resistance in dynes per sec. cm.^{3} was 332 (normal 100). Pulmonary function studies revealed vital capacity of 2,754 cc. (predicted value 3,803 cc.). The residual volume-total lung capacity ratio was 57 per cent (predicted 31 per cent). The maximum breathing capacity (in liters per minute) was 25 (predicted value 94). The index of intrapulmonary mixing alveolar N_2 was 9.7 per cent (predicted value 2.5 per cent). The dead space-tidal volume ratio was 45 per cent (predicted value 30 per cent).

A right upper lobectomy with a pleural tent was performed on December 15, 1952. At operation, the right upper lobe was large and cystic and was devoid of normal pulmonary tissue. The right middle and lower lobes had minimal emphysematous changes. On pathologic section at least one half of the right upper lobe consisted of a soft, cystic, almost structureless mass which appeared to be totally composed of air filled spaces with a thin membranous capsule. Microscopically, there was moderate intimal thickening of the large arteries. The alveoli were dilated with some interalveolar fibrosis. The diagnosis was emphysema and fibrosis with arteriosclerosis of the pulmonary arteries.

Four months later, the conventional frontal roentgenogram of the chest (Fig. 3*C*) revealed some deviation of the trachea to the right and a dense right apex due to a pleural tent. The right lung appeared uniformly well aerated while the left upper lung field was overdistended with increased radiolucency.

Comment. Angiocardiographic studies in this case demonstrated bullae in both upper lobes with distortion and compression of the vasculature of the lower lobes but without the pattern of generalized emphysema. These findings with the clinical and functional studies of the lung predicted that surgery would be beneficial, and so it proved. The patient returned to work; seven years later he was well despite the remaining left upper lobe bulla.

Case iv. *Bilateral bullous emphysema; improved by bilateral upper lobectomy.* A fifty-six year old man (N.Y.H. No. 541430) was examined on June 12, 1949, because of severe dyspnea of three years' duration. During the previous six months he had had a chronic, persistent and productive cough. On physical examination the posteroanterior diameter of the chest was markedly increased and there were inspiratory and expiratory rales over both upper lobes. The conventional frontal roentgenogram of the chest showed marked radiolucency in the upper halves of the lung fields (Fig. 4*A*). Angiocardiograms on May 19, 1949, revealed compression of the lower lung field vasculature with markedly decreased vasculature of the upper lungs (Fig. 4*B*). At operation on June 17, 1949, the left upper lobe was completely replaced by several large bullae which compressed and displaced the lower lobe into the inferior portion of the thoracic cage. Left upper lobectomy was performed. A large bulla was excised from the apical segment of the lower lobe and a pleural tent made. Pathologic study of the left upper lobe showed multiple bullae varying from 1.5 to 9 cm. in diameter. Microscopically, the cyst walls consisted of collagenous connective tissue lined in some areas by cuboidal epithelium. The adjacent lung parenchyma had dense bands of fibrous tissue traversing it. The final diagnosis was bullous emphysema and fibrosis.

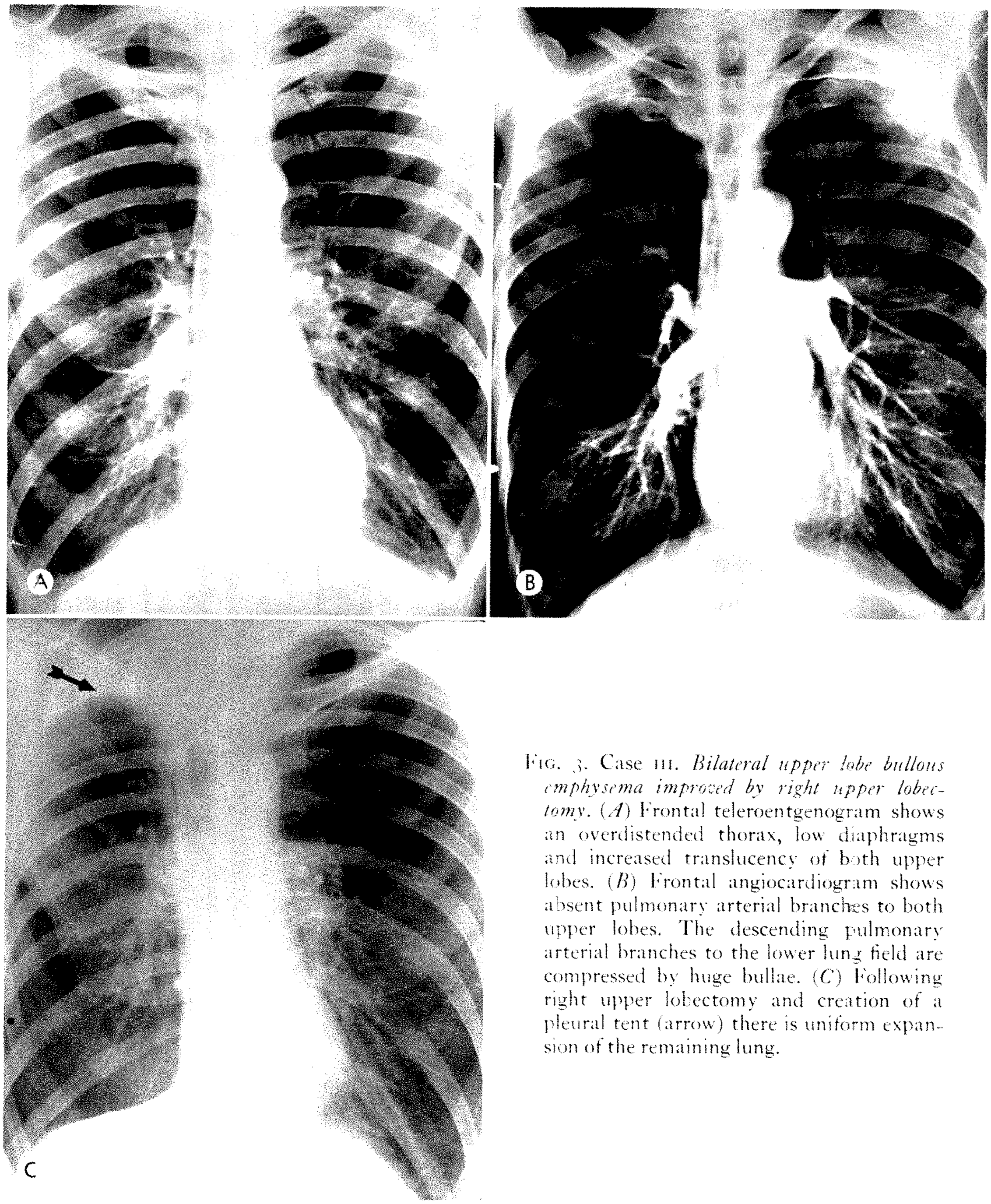


Fig. 3. Case III. *Bilateral upper lobe bullous emphysema improved by right upper lobectomy.* (*A*) Frontal teleroentgenogram shows an overdistended thorax, low diaphragms and increased translucency of both upper lobes. (*B*) Frontal angiocardiogram shows absent pulmonary arterial branches to both upper lobes. The descending pulmonary arterial branches to the lower lung field are compressed by huge bullae. (*C*) Following right upper lobectomy and creation of a pleural tent (arrow) there is uniform expansion of the remaining lung.

Postoperative angiocardiograms (March 9, 1950) showed the density at the left apex due to the pleural tent (Fig. 4*C*). There was increased radiolucency at the left base and marked radiolucency in the upper two-thirds of the right lung with compression and displacement of the vasculature into the lower portion. The pulmonary vessels of the left lung appeared uniformly distributed, decreased in number and caliber.

For four years the patient was well and able to do regular work but gradually became totally disabled because of dyspnea. On April 12, 1954, a right upper lobectomy was performed. Pathologic study revealed the pleural surface to be

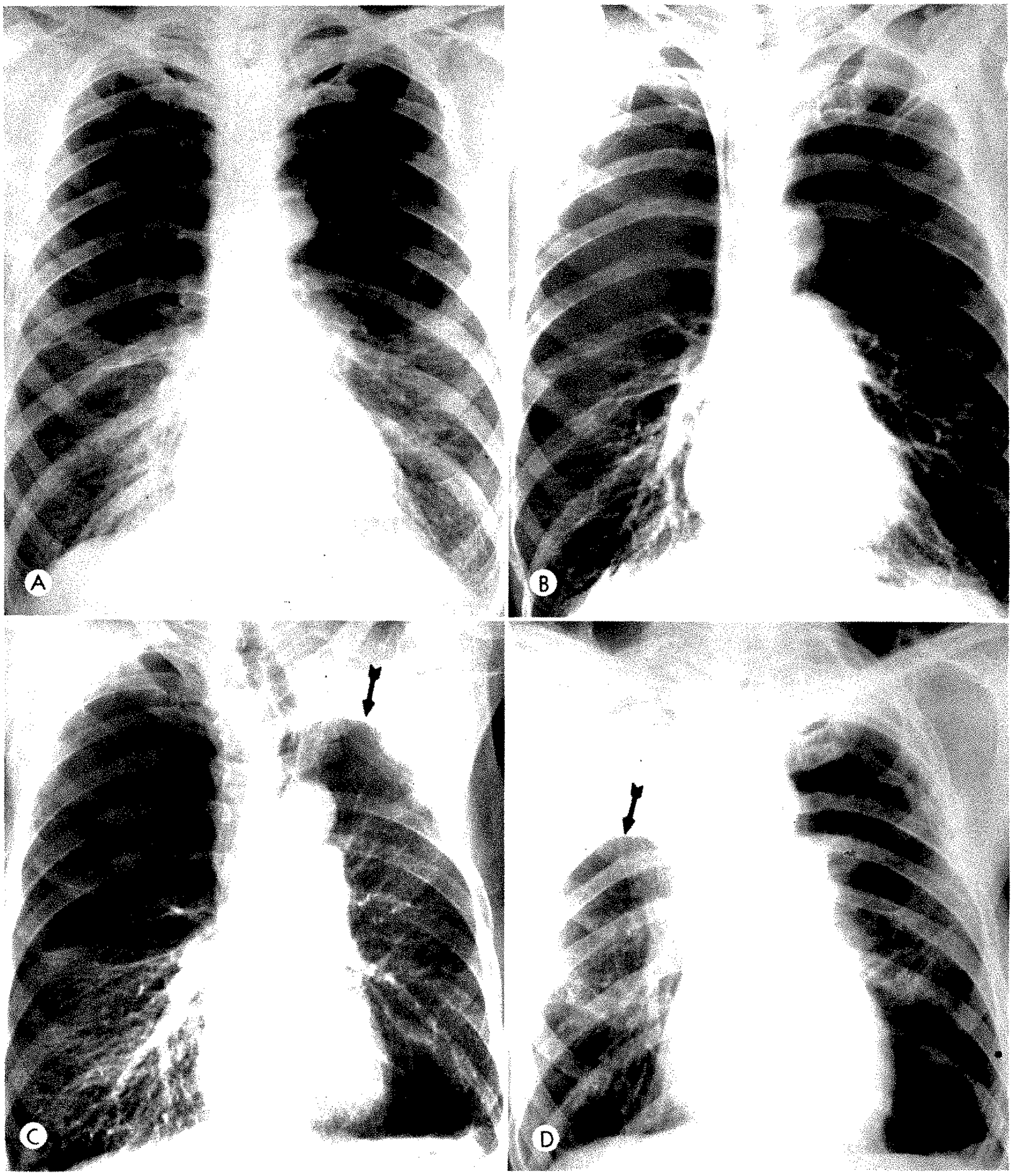


FIG. 4. Case IV. *Bullous emphysema improved by bilateral upper lobectomy.* (*A*) Conventional frontal roentgenogram shows huge bilateral bullae of both upper lung fields with compression of the lower lung fields. (*B*) Angiocardiogram shows absence of pulmonary arterial circulation of the upper lobes with marked compression of the pulmonary vasculature of the lower lobes. (*C*) Following left upper lobectomy and formation of a pleural tent (arrow), the left pulmonary arterial tree was no longer compressed. Note the appearance of a large left lower lobe bulla. Despite this, clinical improvement resulted. (*D*) Four years later, recurring dyspnea necessitated a right upper lobectomy and pleural tent formation (arrow). This was followed by improvement and return to work, now of five years' duration.

thickened and with many large bullae. The cut surface had a honeycomb appearance involving one half of the specimen. Marked peribronchial inflammatory infiltration was seen. The final diagnosis was bullous emphysema, bronchiectasis and compensatory atelectasis.

The postoperative conventional frontal roentgenogram of the chest taken on June 17, 1954, disclosed good aeration of the right lung, although a radiolucency at the left base was still noted (Fig. 4*D*). Following this the patient resumed his regular work but died five years later (1959) of emphysema and cor pulmonale.

Comment. Angiocardiography by revealing bilateral upper lobe bullous emphysema without evidence of generalized emphysema strengthened the decision to perform surgery on 2 separate occasions and eventually restored the patient's ability to work for several years.

Case v. *Bilateral bullous emphysema; right pneumothorax cured after excision of bullae and blebs.* A thirty-eight year old woman (N.Y.H. No. 679045) came to the clinic on March 22, 1954, with a history of a previous spontaneous left pneumothorax. On examination the chest was asymmetric and expanded equally. The breath sounds were distant and the lung fields were uniformly resonant. Roentgenoscopy revealed a large cyst in the upper third of the right chest which increased in size on deep inspiration and decreased with expiration. Another large cyst in the lower half of the left chest was unaltered by respiration. Review of previous roentgenograms beginning in 1944 showed a progressively enlarging cyst at the left base, whereas the cyst in the right upper lung field had been unchanged in size during a ten year period. Angiocardiography (Fig. 5*A*) on May 4, 1954, showed a huge cyst occupying the lower two-thirds of the left lung which distorted and compressed the left lower pulmonary vasculature. A smaller cyst was also present in the upper third of the right lung. The pulmonary vasculature appeared sparse in the upper lobes. Pulmonary function data revealed the vital capacity to be 2,291 cc. (predicted value 2,810 cc.). The maximum breathing capacity in liters per minute was 98 (predicted value 83).

Surgery on the left side was advised but refused by the patient. She was re-admitted on June 26, 1956, with complaints of mild dyspnea on exertion and a chronic nonproductive cough of one year's duration. Just prior to admission

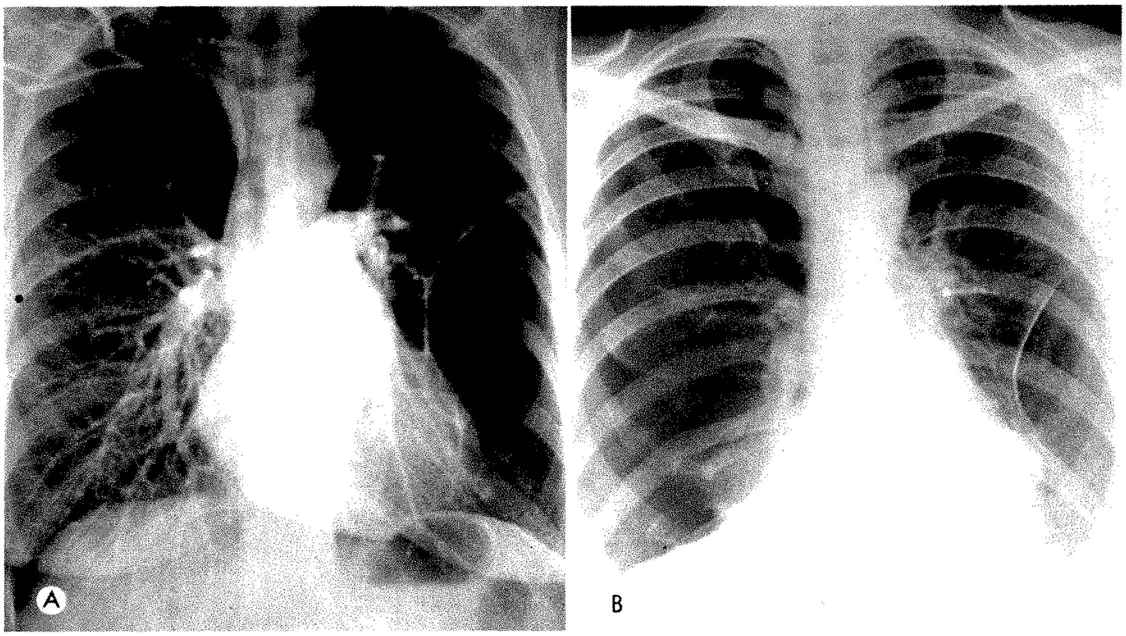


Fig. 5. Case v. *Bilateral bullous emphysema complicated by right spontaneous pneumothorax that failed to re-expand following suction.* (*A*) Frontal angiocardiogram shows bullous emphysema of both lungs causing classic compression of the remaining lung. (*B*) Two years later, a right spontaneous pneumothorax failed to re-expand after suction; excision of cysts restored pulmonary function.

the dyspnea suddenly became worse and there was chest pain. A frontal chest roentgenogram revealed 70 per cent pneumothorax on the right (Fig. 5*B*). Intercostal tube drainage failed to reduce the pneumothorax and so surgical treatment was advised. At thoracotomy, there was a liter of serous fluid in the right chest; a 10×4 cm. bulla was found in the apical segment of the upper lobe. The pleural surface of all lobes of the lung was studded with multiple (2–3 mm.) emphysematous blebs while on the inferior border of the middle lobe there were several large (2 cm.) blebs. A 6×5 cm. bleb was also present in the lateral basal segment of the lower lobe. Many blebs were excised; others were transfixed and covered with pleural grafts. Following this the patient made an uneventful recovery. On re-examination a year later, dyspnea was no longer present although the left lower lobe cyst remained.

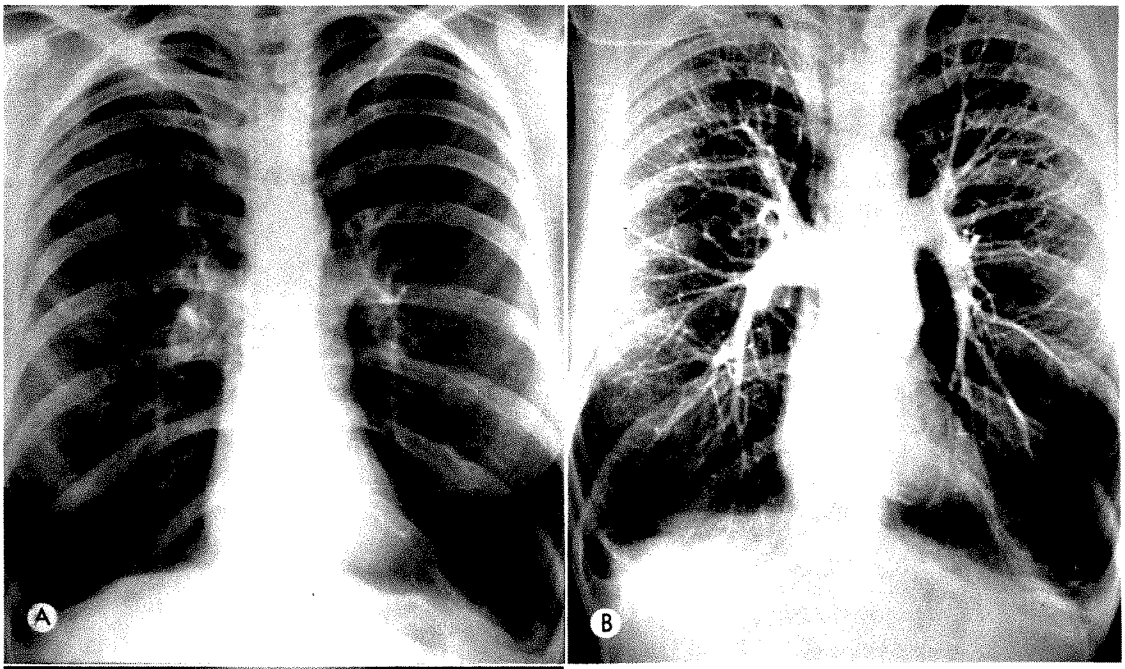
Comment. This case illustrates a common complication of bullous emphysema—spontaneous pneumothorax. The enlarging cyst in the left lung and the symptomatic state of the patient warranted surgical intervention when she was first seen. Later, the spontaneous pneumothorax on the opposite side with failure to secure re-expansion after suction drainage made surgery necessary in the right side.

CASE VI. *Generalized and bullous emphysema; failure to improve following left lower lobectomy.* A thirty-nine year old housewife (N.Y.H. No. 389560) had had dyspnea and a productive cough for seven years. Six years previously she had been admitted to another hospital for a spontaneous right hydropneumothorax. Recently, the cough had been productive of one cup of greenish sputum daily. Physical examination showed moderate respiratory distress with difficulty in expiration. There was no cyanosis or edema. The anteroposterior diameter of the thorax was increased and the respiratory rate was rapid with increased use of accessory muscles of respiration. The diaphragms were low; the breath sounds were distant and a few inspiratory rales were present at both bases. The chest was hyper-resonant throughout. The conventional frontal roentgenogram of the chest showed markedly distended lungs with extremely low diaphragms and increased radiolucency of the lower lung fields (Fig. 6*A*).

Angiocardiograms (Fig. 6*B*) made on March 2, 1953, showed moderate enlargement of the pulmonary artery and main branches. The pulmonary vascular tree appeared wiry. In the lower lobes the pulmonary arterial vasculature appeared diminished. There was slight distortion and compression of the peripheral vascular pattern in the left lower lung field (Fig. 6*B*). Pulmonary function studies were done January 17, 1950, and revealed the vital capacity to be 2,800 cc. (predicted value 3,286 cc.), while the maximum breathing capacity in liters per minute was 56 (predicted value 92). On April 8, 1953, the vital capacity was 1,553 cc. and the maximum breathing capacity was 34. The O_2 saturation was 91.8 per cent (predicted value 97 per cent). After exercise the O_2 saturation was 85.7 per cent. The CO_2 tension was normal at rest and exercise. On December 3, 1953, the vital capacity was 1,253 cc. and the maximum breathing capacity was 22.

At operation, April 5, 1954, the left lower lobe was distended and compressed the left upper lobe into a third of its normal volume. Some emphysematous changes were visible in the left upper lobe, particularly along the lower borders and in the lingula. Left lower lobectomy was performed and a pleural tent was made. On pathologic section, bullae were most prominent in the posterior and medial aspect of the left lower lobe. The lung tissue occupying the lower half of the lobe was very emphysematous and spongy in appearance. Fifteen days following operation congestive failure developed. Figure 6*C* is the postoperative roentgenogram. Severe dyspnea persisted and pulmonary function studies on May 23, 1955, revealed the maximum breathing capacity to be only 19. The O_2 saturation at rest was 89 per cent; with mild exercise it was 85 per cent. The patient continued to be dyspneic, developed right sided heart failure, fever, and died on December 13, 1955.

Autopsy showed marked generalized emphysema of the right lung. The largest bulla was only 5 mm. in diameter. However, on the left, the lowermost portion of the upper lobe contained many large bullae. One measured 6×3×3 cm. and another 6×6×8 cm. The remainder of the left upper lobe was sponge-like in consistency; the largest bulla in the upper portion of the lobe was 4 mm. in diameter. Microscopically, the alveolar walls were slightly thickened; a few alveoli contained hemosiderin-filled macrophages. The basement membranes



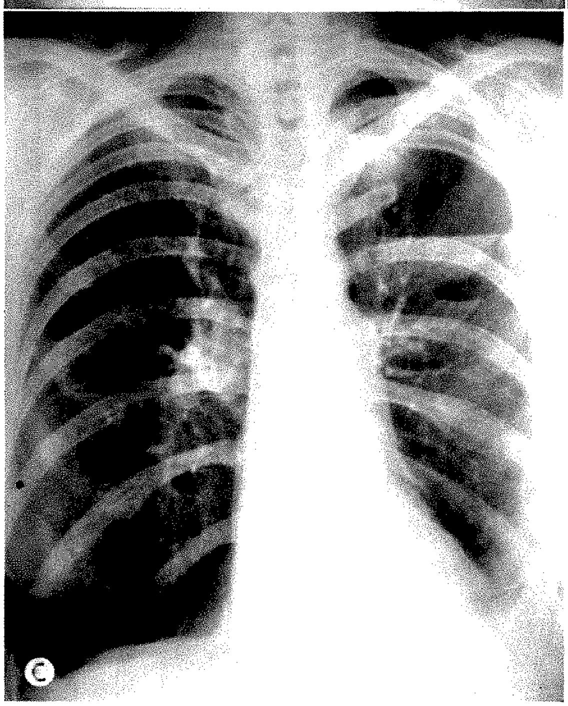


FIG. 6. Case VI. *Generalized and bullous emphysema unrelieved by left lower lobectomy.* (*A*) Conventional roentgenogram showing overdistention of the lungs with increasing translucency of the lower lobes. (*B*) Frontal angiocardiogram reveals the wiry pulmonary arterial pattern of generalized emphysema of the lower lobes with bullous emphysema at the bases. (*C*) Conventional roentgenogram following lobectomy shows the left lung pulmonary vascular pattern to be improved. However, this was not followed by clinical improvement.

of the bronchioles were thickened. There was evidence of acute and chronic bronchitis in the right middle and lower lobes. The small arteries were slightly thickened throughout and there was considerable atherosclerosis. The diagnosis was advanced generalized pulmonary emphysema in all lobes of the lungs with bullous emphysema in the lower portion of the left upper lobe. The heart weighed 458 gm. and there was marked right sided hypertrophy and dilatation. A ruptured diverticulum and generalized peritonitis were the immediate causes of death.

Comment. The degree of functional deficit demonstrated by the physiologic data

correlated with the localized nature of the bullae and the signs of generalized emphysema visualized on the angiocardiograms accurately predicted that little improvement could be expected after surgery. Although the localized bullous emphysema in the left lower lobe was removed surgically, the relentless progress of the generalized emphysema was eventually fatal.

Case vii. *Bullous emphysema of the entire right lung improved by pneumonectomy.* A sixty-six year old man (N.Y.H. No. 793691) was admitted April 23, 1958, with a history of dyspnea of ten years' duration. Twenty years prior to admission he had had a right spontaneous pneumothorax which was treated by repeated needle aspirations. One week prior to admission there were expectoration of blood and pain in the right chest. On physical examination the anteroposterior diameter of the thorax was increased. There was dullness over the right posterior upper chest, and decreased breath sounds with occasional expiratory wheezes were heard over the entire right chest; the respiratory rate was rapid. The pulse rate was regular, rate 94, and the blood pressure was 210/100 mm. Hg; the heart was not enlarged. The conventional frontal roentgenogram of the chest (Fig. 7*A*) showed overdistention of the right lung with downward displacement and flattening of the right diaphragm. There were large cysts in the right lung and extensive fibrosis in the right lower lung fields. Frontal laminagrams of the chest clearly showed the large cysts of the right lung (Fig. 7*B*). Lateral laminagrams also showed that the large cysts occupied almost the entire right lung (Fig. 7*C*). Serial angiocardiograms (Fig. 7*D*) on April 24, 1958, showed abrupt termination of the pulmonary arterial vasculature at the right hilus. The left pulmonary artery was well visualized and the peripheral circulation appeared decreased.

On April 28, 1958, a right pneumonectomy was performed. The major portion of the entire right lung contained bullae varying from 1 to 10 cm. in diameter. One large cyst dissected between the bronchus and the right pulmonary artery had almost completely shut off the circulation to the right lung. Bullae also extended into the mediastinum where they compressed and displaced the esophagus. On pathologic section, the right lung appeared markedly lobulated with many bullae and blebs over the entire surface. There was extensive pleural thickening. Microscopically, the pulmonary arterial walls were thickened. The alveolar walls were thin and the alveoli were distended in many areas. The diagnosis was extensive bullous emphysema and interstitial fibrosis. The patient has remained well for two years.

Comment. Laminagraphy showed the changes of advanced bullous emphysema in the right lung to advantage, whereas angiocardiography revealed almost complete obstruction of blood flow to the right lung due to compression of the right pulmonary artery by bullae. These studies accurately foretold the benefit of pneumonectomy.

Case viii. *Bilateral bullous emphysema with spontaneous left pneumothorax; improved by segmental resection.* A fifty-nine year old man (N.Y.H. No. 657937) had had sudden onset of severe dyspnea and pain in the left chest six days prior to admission in December, 1955. On physical examination, the chest was symmetric and the left chest was hyper-resonant. The breath sounds in the left upper anterior chest were increased but were decreased throughout the remainder of the left chest. The pulse rate was 70 and regular and the blood pressure was 180/90 mm. Hg. Conventional roentgenograms of the chest showed a 50 per cent pneumothorax in the left lung in addition to large cysts in both upper lobes. Two years earlier (1953) the conventional frontal roentgenogram of the chest showed large cysts occupying the upper one-third of both lungs (Fig. 8*A*). Angiocardiograms at that time (June 12, 1953) revealed the entire right pulmonary arterial tree to be compressed into the lower two-thirds of the chest (Fig. 8*B*). The vasculature of the upper one-third of the left lung was also compressed laterally. Other angiocardiographic studies on December 6, 1955 (Fig. 8*C*) showed a left pneumothorax with almost complete collapse of the left lower lobe. The left upper lobe vasculature appeared compressed laterally to a greater extent than on the previous study, whereas the vasculature in the right chest appeared unchanged in the two year interval.

Pulmonary function studies on December 7, 1955, revealed the vital capacity to be 3,010 cc. (predicted value 3,635 cc.). The maximum breathing capacity was 65 (predicted value

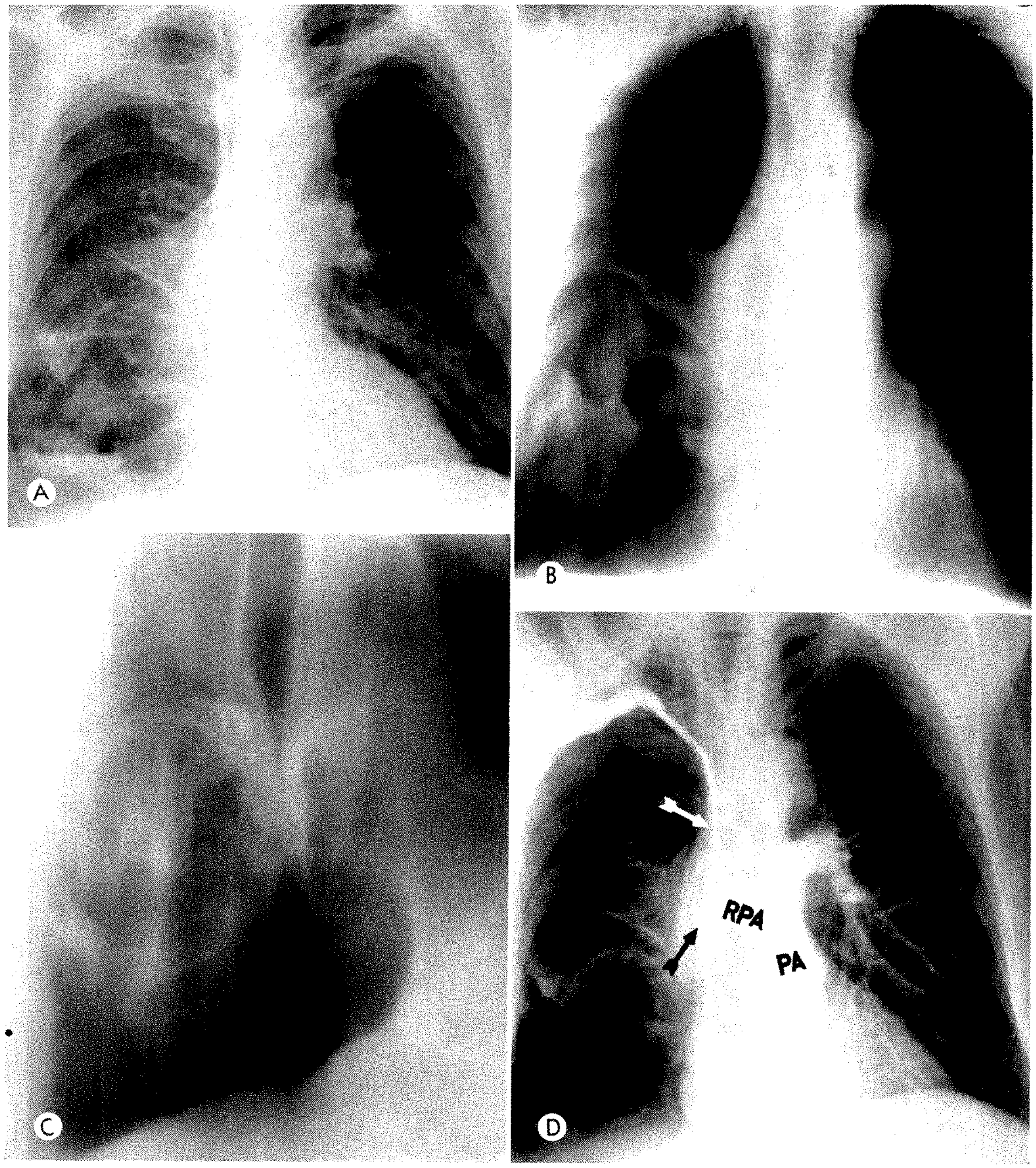


Fig. 7. Case vii. *Bullous emphysema of the right lung, improved by pneumonectomy.* (*A*) Frontal roentgenogram shows multiple bullae of the right lung, especially at the base. (*B*) Frontal laminagram shows numerous cysts in the right lower lobe. (*C*) Right lateral laminagram reveals the size of the bullae. (*D*) Frontal angiocardiogram shows narrowing of the superior vena cava (arrow) and absence of right pulmonary arterial blood flow (arrow). PA is the pulmonary artery and RPA is the right pulmonary artery.

103). At operation on December 12, 1955, a tension pneumothorax was present and there was marked overdistention of the apicoposterior segment of the left upper lobe due to numerous large bullae. A segmental resection was done and a pleural tent formed. In the remaining lung there were three small blebs. On pathologic study many blebs measuring 2–3 cm. in diameter were present on one margin of the lung segment. There was marked fibrous thickening around some of the bronchioles and along the alveolar walls. The pleura was also thick-

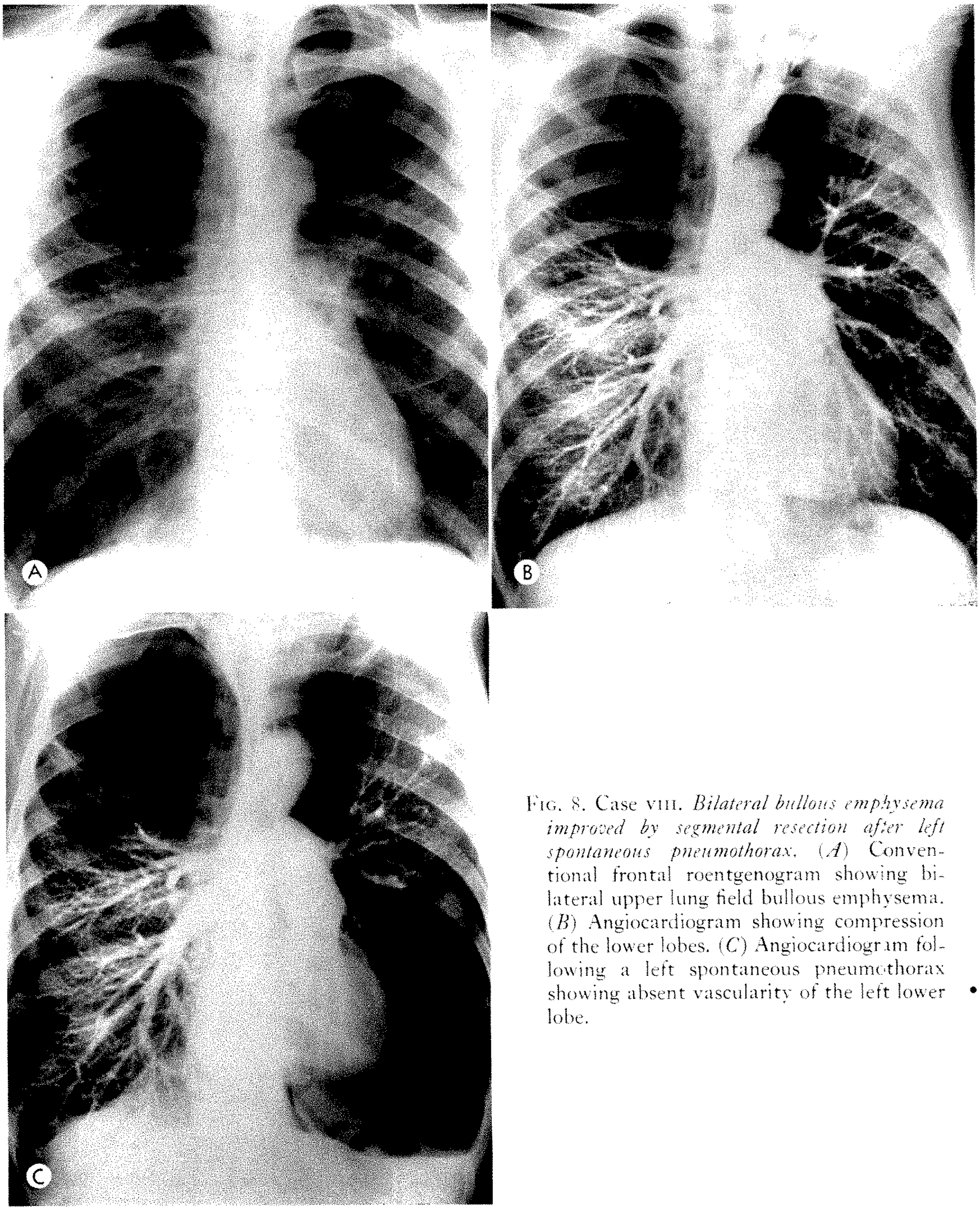


Fig. 8. Case VIII. *Bilateral bullous emphysema improved by segmental resection after left spontaneous pneumothorax.* (*A*) Conventional frontal roentgenogram showing bilateral upper lung field bullous emphysema. (*B*) Angiocardiogram showing compression of the lower lobes. (*C*) Angiocardiogram following a left spontaneous pneumothorax showing absent vascularity of the left lower lobe.

ened. The diagnosis was bullous emphysema and fibrosis.

Postoperative frontal roentgenograms of the chest showed a re-expanded left lung with a pleural tent at the apex. There was a 4×3 cm. cyst just beneath the pleural tent. The cyst in the right upper lung field appeared much smaller than on previous studies (Fig. 8*D*). Repeat angiocardiograms on April 18, 1957 (Fig. 8*E*) showed a moderately enlarged pulmonary artery and branches. The sparse right upper lobe vasculature was compressed laterally but to a much lesser extent than in the previous studies. A cyst just below the left pleural tent

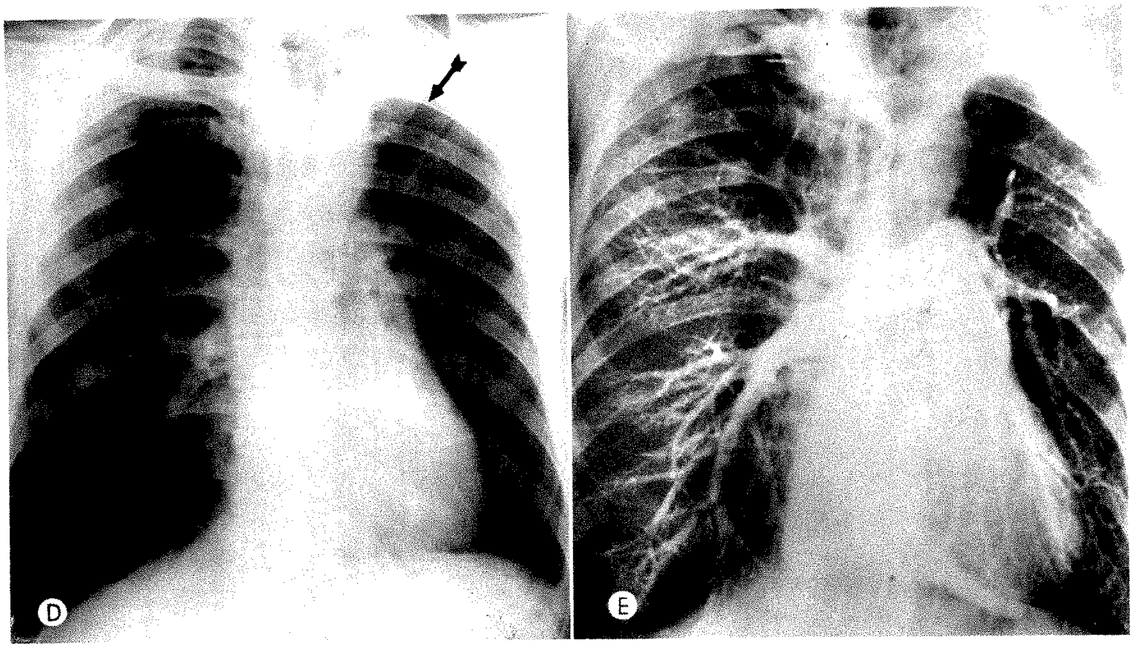


FIG. 8. Case VIII. (*D*) Improvement followed segmental resection of the left lung and formation of a pleural tent (arrow). (*E*) Angiocardiogram following operation shows return of the normal pulmonary arterial pattern in the left lung.

was also seen. Following operation the patient became asymptomatic and resumed work.

Comment. Although angiocardiography indicated that the bullous emphysema was more extensive on the right side, spontaneous pneumothorax on the left side necessitated surgical intervention. Spontaneous improvement in the right lung made further surgery unnecessary.

DISCUSSION

Bullae (pneumatoceles) are hyperinflated intrapulmonary cavities produced by the marked distention of a defect in the pulmonary parenchyma.[7,14] Blebs are similar to bullae except that they are subpleural rather than intraparenchymal; both have indirect bronchial communication and physiologically exhibit air trapping.[16] Pulmonary cysts are congenital in origin, are lined by cuboidal or columnar epithelium and have frank bronchial communications which are frequently partially filled with fluid.

The etiology of pulmonary emphysema is not as yet completely defined. It is generally agreed that the primary lesion is one of bronchiolar obstruction with subsequent air-trapping distal to the obstruction. There is loss of pulmonary elasticity and finally there is disruption of the alveolar walls with bulla formation. The cause of the obstructive phenomena is attributed to a variety of histopathologic changes. Amberson and Spain,[1] and Spain and Kaufman[27] have surmised that chronic bronchiolitis and peribronchiolitis involving terminal bronchioles result in stiffening of the walls and narrowing of the lumina. The inflammation and subsequent fibrosis involve the musculature and elastic components and interfere with the tone and action of the involved bronchiolar walls. Inspiration tends to expand the narrowed bronchioles allowing passage of air into the respiratory alveoles and alveoli. On expiration, however, the caliber of the narrowed bronchioles is further reduced and delays emptying of the alveoli of the involved lobules. This check-valve mechanism tends to dilate alveoli. Because the chronically distended alveoli receive a diminished blood and oxygen supply,

atrophy and disruption occur.[12] The presence of tenacious mucus in the bronchial passages also aggravates the mechanism.

McLean[16] proposed that obstruction of small bronchioles with mucous plugs occurs in acute bronchiolitis. If obstruction persists there may eventually be obliteration of the bronchiole, particularly in the proximal order of respiratory bronchioles. During the phase of obstruction there is collateral ventilation of the distal alveoli through the alveolar pores of Cohn. During inspiration there is good collateral ventilation of the alveoli in the regions distal to the obstruction while in expiration the channels become narrow and tortuous and cause some degree of air trapping. Recurrent infections with subsequent bronchiolar obliteration promote and potentiate air trapping with its associated alveolar distention. There is then reduced blood flow in the capillaries of the collaterally ventilated alveolar walls due to distention of the alveoli by the increased pressure of the trapped air. With decreased blood flow, there are decreased oxygen supply and nutritive factors with subsequent loss of elasticity and atrophy of the alveolar walls. The alveolar pores of Cohn increase in size at the expense of the wall and are reduced in thickness. As the process continues many of the septa break and a large bulla is formed.[12] The most severe emphysematous changes are seen in sites where collateral ventilation is restricted by tissue impervious to air, near the pleura or scar tissue.

Peirce and Dirkse[20] in 1937 described the development of pneumatoceles as complications of lobar or lobular pneumonia. They postulated a persistent check-valve effect in the bronchus due to nonresolution of the initial inflammation of the bronchus or a subsequent distortion by the dilated air spaces. In only one of their 4 cases did the pneumatoceles disappear despite almost complete clearing of the surrounding parenchymal infiltrations. Other obstructive factors have also been proposed to explain special instances of localized emphysema. Shaw[25] noted that the bronchi of the affected lobes were abnormally flaccid and suggested that localized chondromalacia of the bronchus results in expiratory bronchial collapse with obstructive emphysema distal to the block. Ferguson and Neuhauser[9] described absent cartilaginous rings in the left main bronchus of 2 cases with emphysema of a whole lung. Robertson and James[22] reported a case wherein a large vein hooked around the right upper lobe bronchus resulting in narrowing of the bronchial lumen. In another case, valve-like mucosal flaps were present in the right upper lobe bronchus and were considered responsible for the obstructive distention of the lobe. The role of chronic bronchiectasis, asthma, attacks of bronchiolitis and pneumonitis in bullous emphysema is well known and has long been stressed.[4]

History and physical examinations in association with chest roentgenograms are important for evaluation of pulmonary emphysema. Roentgenoscopy of the chest also should be performed to estimate diaphragmatic, mediastinal and thoracic cage mobility. Changes in radiolucency of special areas of the lung during respiration should be surveyed to evaluate the degree of air trapping in bullae. The amount of compression of surrounding lung parenchyma by bullae should also be noted. Bronchoscopy in selected patients with emphysema helps to rule out foreign bodies or endobronchial lesions. Bronchography is hazardous, especially when there is severe dyspnea. It is sometimes helpful in differentiating cystic bronchiectasis, congenital pulmonary cysts[8] and abnormal transradiancy of one lung[13] from bullous emphysema. Laminagraphy has also been useful for locating bullae (Fig. 7, *B* and *C*).

Cardiopulmonary and bronchospirometric studies have provided physiologic data for clarifying functional deficits in patients with emphysema. The arterial O_2 saturation, the degree of CO_2 retention, the maximum breathing capacity, the alveolar index and the residual volume to lung capacity ratio are all helpful data. In bullous

emphysema relative hypoventilation of some compressed normal parenchyma, although well perfused, causes elevated venous admixture ratios which augment hypoxia and hypercapnia. Abnormal ventilation perfusion relationships in both generalized and localized bullous emphysema with lung compression can produce hypoxia and even hypercapnia. A high residual volume, poor alveolar mixing and a decreased maximum breathing capacity could be due to bullae communicating with the lung, a high degree of air trapping, to bullae compressing normal adjacent parenchyma and obstructing ventilation, or to generalized emphysema. The specific differentiation of patients with localized bullous emphysema with compression of either relatively normal or emphysematous adjacent lung parenchyma from those with generalized pulmonary emphysema on the basis of physiologic data alone may be difficult.[2,3,10,11,26]

The patients with bullous emphysema who may be benefited by surgery may be classified into four groups: bullae with recurrent pneumothorax on one or both sides;[5,6] infected bullae (tuberculous or nontuberculous);[23,24] bullae increasing in size; and bullae with progressive symptoms of dyspnea, chest pain, cough and sputum. Patients in the first three groups can be frequently found to be suitable for surgery without the need of angiocardiographic study. In the fourth group, the basic problem is how to differentiate the patients whose symptoms are due to bullous emphysema from those with symptoms related primarily to generalized pulmonary emphysema.

Angiocardiography by outlining the pulmonary vasculature is useful for determining the degree of generalized and bullous types of emphysema. For example, in generalized emphysema (Fig. 1, *B* and *C;* and 2*B*) the characteristic "winter tree pattern" is evident. The pulmonary arterial branches taper abruptly in the midzone and continue in a wiry pattern causing delayed blood flow. Bullae (Fig. 3*B;* 4, *B* and *C;* 5*A;* and 8, *B*, *C* and *E*) are avascular and distort and compress the pulmonary arterial tree. The degree of functional impairment of the surrounding parenchyma can thus be judged. Combined generalized and bullous emphysema may be difficult to evaluate even with angiocardiography (Fig. 6*B*). The correlation of the patient's clinical status, pulmonary functional deficits, degree of bullous involvement and the extent of generalized emphysema seen angiocardiographically are the best criteria for selecting the patient suitable for surgery.

SUMMARY AND CONCLUSIONS

Eight patients with disabling emphysema were selected to illustrate the role of angiocardiography in the diagnosis and treatment of their disease. In generalized emphysema, the pulmonary vasculature resembles a "winter tree" pattern in that there is tapering and constriction of the peripheral pulmonary arterial tree. In bullous emphysema, there is diminution or absence of pulmonary vasculature because of the cysts. More important, though, is recognition of compression of the neighboring lung by the cysts. For it is reasonable to hope that the removal of useless portions of the lung will not only benefit pulmonary function but that the restoration of previously compressed pulmonary segments and lobes will improve it. Furthermore, if it can be proved that hypoxia and cor pulmonale are due to localized bullous emphysema, the indication for surgery is strengthened.

Angiocardiography by revealing the pulmonary vasculature readily discloses the patterns of generalized and bullous emphysema and also shows the state of the adjacent circulation. In a series of 8 cases, 2 patients had advanced generalized emphysema which overshadowed the bullous changes and contraindicated surgery. In 5 other patients with predominating bullous emphysema, even though bilateral, angiocardiography aided in evaluating the degree of compression caused by the pulmonary cysts. Surgical improvement fol-

lowed excision of cysts, segments, lobes and lung. In one case, though, excision of a left lower lobe bulla failed to halt the relentless progress of the generalized emphysema.

Various surgical procedures successfully employed in the treatment of 5 patients with bullous emphysema are discussed. These are transfixing blebs and covering with pleura, segmentectomy, lobectomy, and waiting for spontaneous regression of bullae. Dominant principles are the excision of as little normal lung tissue as possible and the prevention of overdistention of the lung by forming a pleural tent.

Although cardiopulmonary and bronchospirometric evaluation of patients provides physiologic data useful for clarifying functional deficits, it cannot always differentiate the patients who are symptomatic primarily due to bullous emphysema from those who are symptomatic due to general emphysema. It is precisely in such situations that angiocardiography becomes important, for, by visualizing the pulmonary circulation, the areas of generalized and bullous emphysema can readily be demonstrated. Furthermore, the effects of the air cysts on the neighboring circulation can be evaluated.

Accordingly, it is concluded that angiocardiography may be useful for the selection of the case likely to be helped by the removal of cysts and bullae. It is also valuable for assessing the improvement in the pulmonary circulation following surgery. Angiocardiography is obviously not necessary in order to decide that operation is needed by patients with bullae who have recurrent pneumothoraces, pulmonary and pleural infections or enlarging bullae.

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ADDENDUM

After completion of this study, two new papers dealing with the roentgen diagnosis of emphysema were published: Fraser, R. C., and Bates, D. V. Body section roentgenography in the evaluation and differentiation of chronic hypertrophic emphysema and asthma. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1959, *82*, 39–62 and Margolin, H. N., Rosenberg, L. S., Felson, B., and Baum, G. Idiopathic unilateral hyperlucent lung: a roentgenologic syndrome. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1959, *82*, 63–75.

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COLLATERAL VENTILATION AND LOCALIZED EMPHYSEMA*

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LOCALIZED pulmonary emphysema presents a problem in the differential diagnosis of its pathogenesis. Awareness of the sequelae of segmental bronchial obstruction and the resultant regional collateral ventilation may simplify the problem. In this paper we shall not concern ourselves with the disease entity of generalized emphysema and its pathogenesis, but rather with localized emphysema in association with obstruction of a segmental or subsegmental bronchus. In 1931 Van Allen and Lindskog[8] demonstrated collateral ventilation in the experimental animal. Subsequently, with the development of the field of thoracic surgery, surgeons became familiar with the phenomenon of transsegmental filling of lung segments through collateral channels, despite the surgical occlusion of the segmental bronchi which normally would ventilate those specific segments. These collateral channels are communications through the interalveolar septa. They are frequently referred to as the pores of Kohn,[4] following his description of them in 1893. The presence of such openings, which permit the passage of gases from alveoli of one segment to those of adjacent segments, has been substantiated frequently in recent medical literature by Macklin,[6] Loosli,[5] and others. In contradistinction to the segments of the lobe, the total lobe is an isolated unit with essentially no collateral channel communications with adjacent lobes. Thus, total lobar bronchial obstruction is invariably followed by collapse of the lobe and absence of aeration.

Clinically, segmental bronchial occlusion may be followed by ventilation of that segment of lung tissue through collateral channels. By virtue of the abnormal mechanics of ventilation through the collateral conduits, emphysematous changes may occur in the lung thus filled. Air drift through the pores of Kohn occurs more readily during expansion of the lung than during contraction. With expansion of the thoracic cage and the lung within it, the pores of Kohn are widely patent. McLean[7] offers the hypothesis that the positive pressure of expiratory contraction of the chest wall and lung causes collapse of the pores of Kohn. In essence, there is a check-valve mechanism at each of these collateral pathways. Thus, localized obstructive emphysema may follow long continued aeration of a portion of lung through collateral channels. Finding this localized emphysema roentgenologically may provide the clue to the basic pathogenetic factor. This would not be detected on routine chest roentgenograms. Further roentgenologic and clinical studies are indicated.

In a previous report[3] we presented 3 clinical cases of localized emphysema secondary to segmental or subsegmental bronchial occlusion. In these cases developmental bronchial fluid-filled cystic abnormalities were shown to be the cause of bronchial occlusion. Churchill[2] has discussed the occasional finding of aerated lung tissue peripheral to bronchi or bronchioles which were replaced by scar tissue in a disease which he termed "obliterative bronchitis or bronchiolitis." McLean[7] has also discussed inflammatory bronchiolar obliteration in the pathogenesis of generalized emphysema.

At this time we wish to describe an *in vivo* experimental demonstration of collateral respiration and to report 2 clinical cases which showed the emphysematous end-result of collateral respiration.

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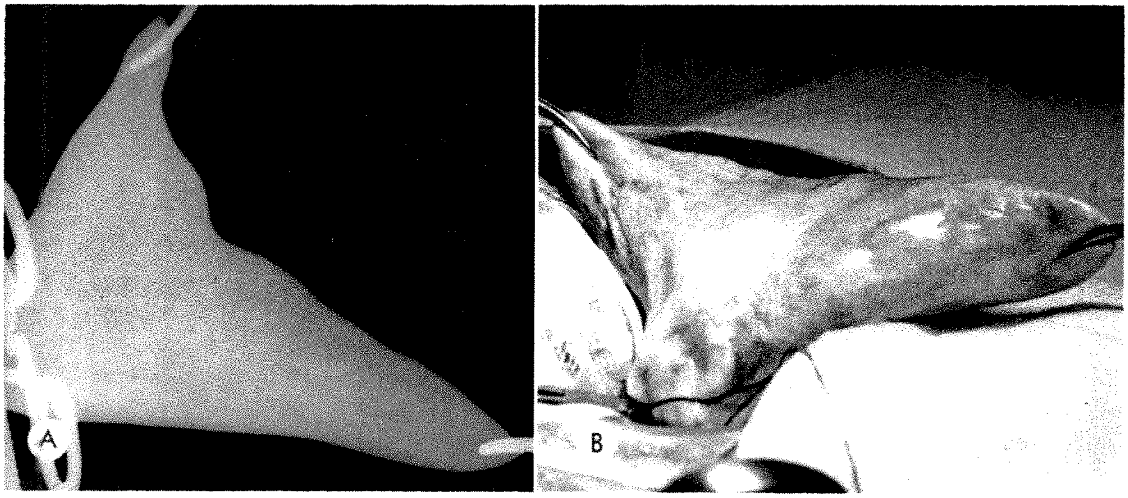

FIG. 1. Roentgenogram (*A*) and photograph (*B*) show total collapse and lack of aeration when the bronchus of the exteriorized lobe is open to atmospheric pressure.

EXPERIMENTAL DEMONSTRATION

A mongrel dog was anesthetized and an endotracheal tube was inserted. Normal ventilation was maintained through the endotracheal tube by the use of a Bird respirator which permitted inspiratory and expiratory cycling at any desired pressure. A thoracotomy was performed and the left lower lobe was lifted through the incision, though its vascular and tracheobronchial continuity was maintained. The segmental bronchi to the lower lobe were identified and isolated. Simultaneous roentgenograms and photographs were taken at various stages of the experimental procedure, but with the different lobar positions required by roentgenologic and photographic needs.

In Figure 1, *A* and *B*, it can be seen that the lower lobe is fully deflated when the endotracheal tube is open to atmospheric pressure.

Figure 2, *A* and *B*, shows that inflation of the lobe is partially obtained by ventilation through a single patent segmental

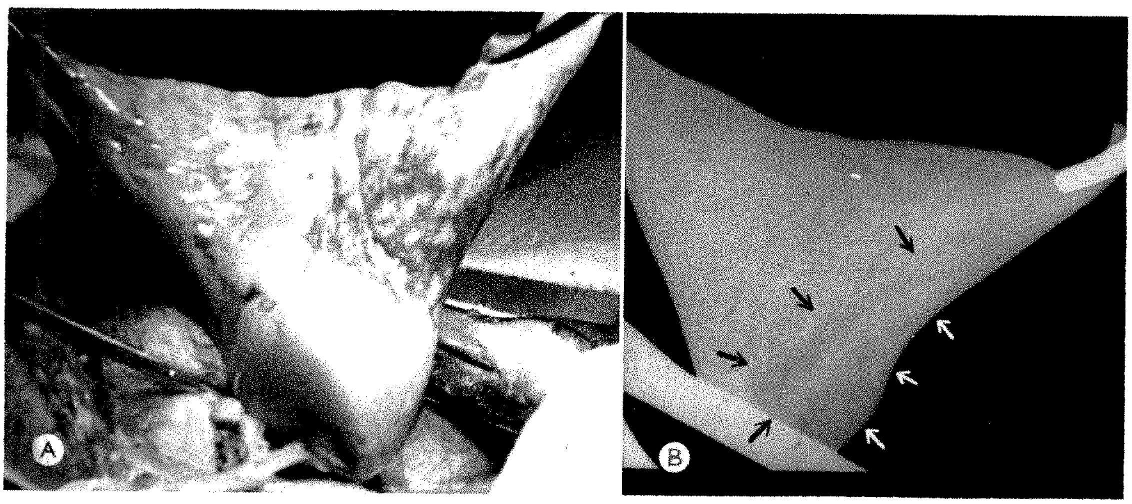

FIG. 2. Aeration of only a single segment is demonstrated. The photograph (*A*) and roentgenogram (*B*) were taken after ten minutes of cycled ventilation at 20 cm. of water pressure through a single patent segmental bronchus.

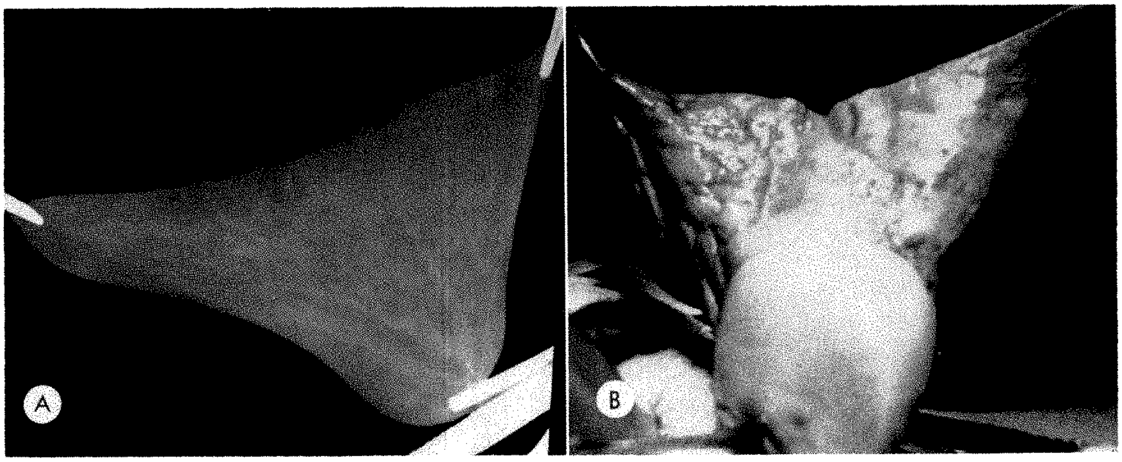

Fig. 3. Roentgenogram (*A*) and photograph (*B*) demonstrate total aeration of one segment and beginning inflation of the other segments. This degree of aeration followed within one minute of cycled ventilation at 40 cm. of water pressure through a single patent segmental bronchus.

bronchus under pressure of 20 cm. of water for a period of ten minutes. The other segmental bronchi of this lobe were clamped and totally occluded. The segment with the patent bronchus rapidly expanded and the segments with the occluded bronchi remained collapsed. Thus the pressure of 20 cm. of water (normal endobronchial pressure of the respiratory cycle varies from minus 2 cm. of water to plus 4 cm. of water during quiet respiration[1]) failed to inflate any segment other than that which had a patent segmental bronchus. There was continued collapse of the segments where the segmental bronchi remained clamped and obstructed.

Figure 3, *A* and *B*, shows inflation being obtained through a single patent segmental bronchus through which pressure of 40 cm. of water was exerted. The other segmental bronchi were occluded by clamping. This roentgenogram and photograph were taken one minute after pressure was applied by using the cycling Bird respirator. They show rapid expansion only of the nonobstructed segment of lung.

In Figure 4, *A* and *B*, taken after five minutes of cycled respiration at 40 cm. of

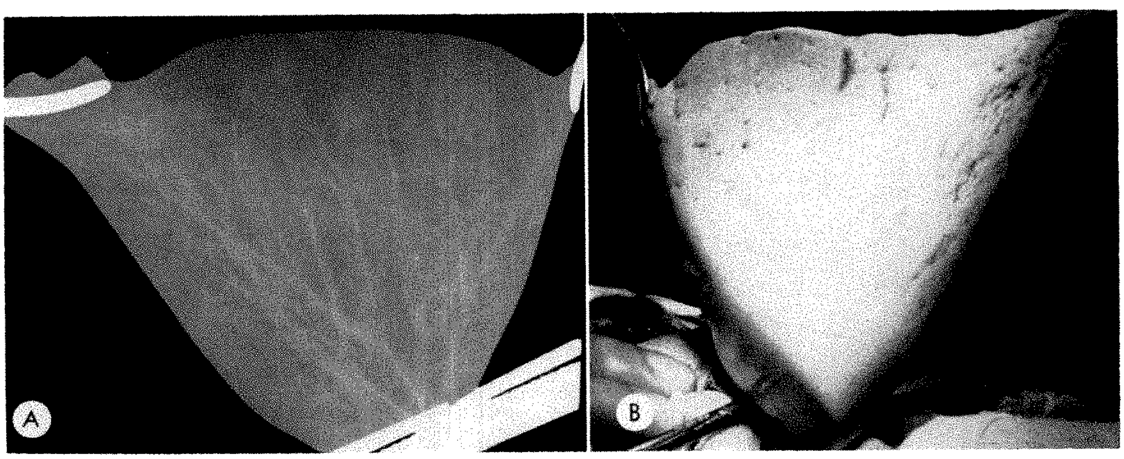

Fig. 4. Roentgenogram (*A*) and photograph (*B*) demonstrate complete aeration of the total lobe. This resulted from cycled respiration at 40 cm. of water pressure through a single patent segmental bronchus for a period of five minutes.

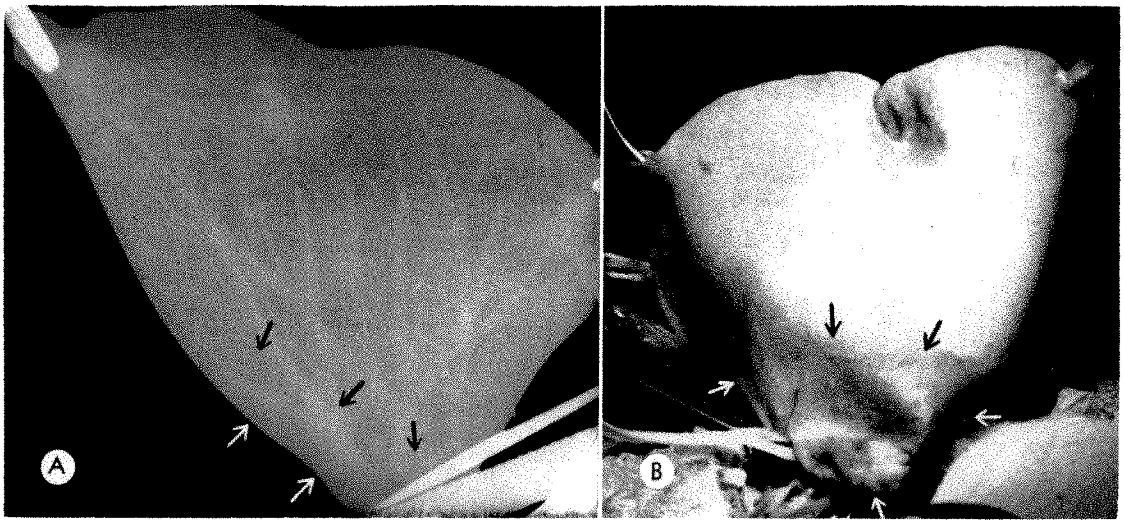

Fig. 5. (*A* and *B*) Following total inflation, deflation was permitted through a single patent segmental bronchus. Only that segment normally ventilated by the patent segmental bronchus collapsed significantly. Collapse of the other segments through the collateral channels was minimal after fifteen minutes.

water pressure, complete aeration of both the obstructed and nonobstructed segments of the lobe is demonstrated. The segments with obstructed segmental bronchi must have been inflated through the collateral channels across the intersegmental planes.

Figure 5, *A* and *B*, shows a totally inflated lobe which was permitted to deflate through a single patent segmental bronchus when the bronchus was exposed to atmospheric pressure. Only the nonobstructed segment collapsed. The segments with obstruction of their bronchi remained inflated. This indicated that, when inflated segments with obstructed bronchi are subject only to the inherent elastic recoil of the lung, the collateral pathways also become obstructed because of their check-valve mechanism. Marked compression must be exerted upon these segments to cause escape of the contained gases through their collateral channels.

REPORT OF CASES

Case I (Fig. 6, *A* and *B*). E.W., a forty-one year old Negro male, presented on a routine chest roentgenogram right upper lobe emphysema and a right parahilar mass of water density. The patient was asymptomatic. He was admitted to the hospital on October 22, 1958 for investigation and treatment.

Bronchoscopy was negative. The orifices of the three segmental bronchi of the right upper lobe were visualized and were normal. Bronchograms showed an obstruction of the bronchus of the anterior segment at a point just beyond its orifice. A large mass was seen adjacent to the obstructed bronchus. Laminagrams demonstrated the large parahilar mass as well as several smaller masses extending anteroinferiorly. The masses were seen to lie within the emphysematous lung tissue. Those segmental bronchi which filled with contrast material branched into normal appearing lung tissue.

On November 12, 1958 thoracotomy revealed that the anterior segment of the right upper lobe was markedly emphysematous and was compressing the apical and posterior segments. The right middle lobe and the right lower lobe showed no emphysematous changes. The parahilar mass contained clear viscid fluid. The lumen of the cystic mass was not in continuity with the tracheobronchial tree proximally or distally. There were several similar but smaller cysts more peripherally in the lung of the same segment. The bronchus of the anterior segment ended blindly at the proximal end of the cystic mass. The right upper lobe was excised. Microscopic sections showed bronchial cystic spaces lined by either columnar or pseudostratified columnar epithelium which rested upon laminated layers of fibrous tissue. There was no cartilage in the fibrous tissue. The surrounding pulmonary parenchyma was ex-

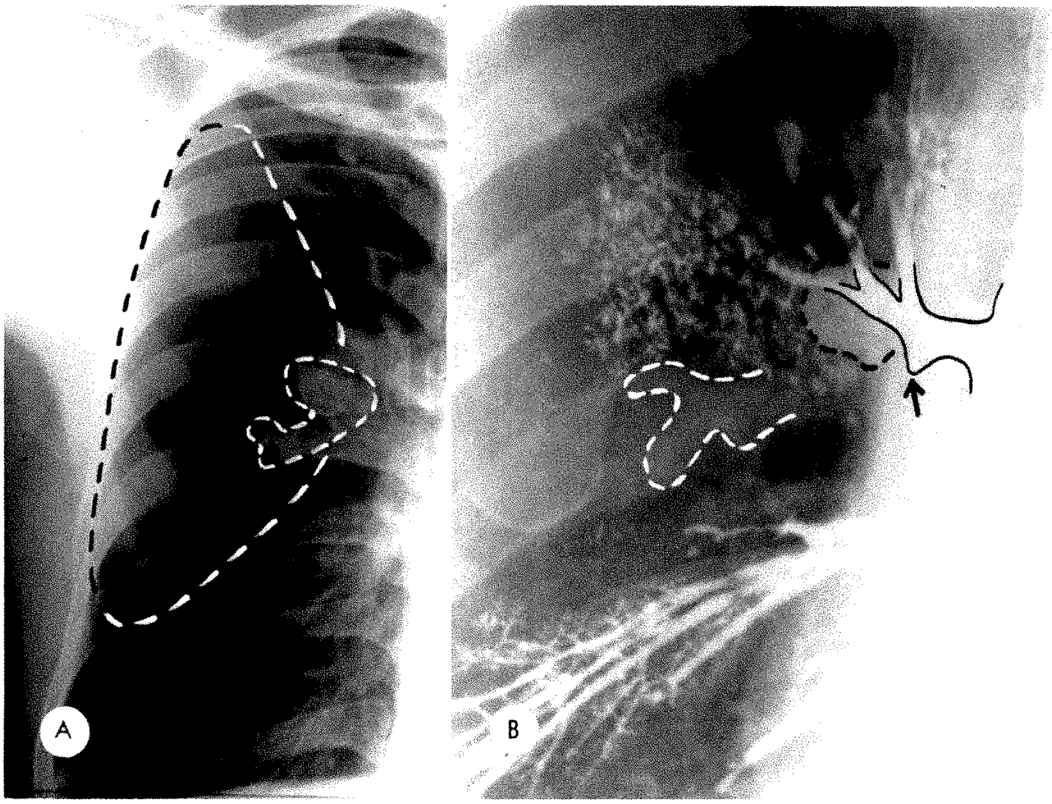

FIG. 6. Case I. (*A*) The mucocele is demonstrated lying within a localized area of emphysema. (*B*) The stump of the anterior segmental bronchus is shown. Adjacent to this lies the branched mucocele surrounded by emphysematous tissue.

tremely emphysematous and contained very few widely scattered pigment-containing macrophages. There were some adjacent regions where the pulmonary parenchyma was atelectatic; here the bronchi were normal in caliber and architecture.

In this patient the anterior segmental bronchus was totally occluded, secondary to anomalous deformities. Collateral ventilation maintained aeration of the segment, causing, ultimately, emphysematous changes.

Case II (Fig. 7, *A–D*). R.D.S., a twenty-five year old white male, presented on a routine chest roentgenogram a small right parahilar mass and peripheral to this an area of pulmonary emphysema. He was asymptomatic. The similarity of the roentgenographic appearance to that previously seen suggested the diagnosis of pulmonary cyst or mucocele in association with pulmonary emphysema.

The roentgenologic examination showed: (1) a 1.5 cm. parahilar mass with an air-fluid level within it on the routine upright roentgenogram. The lateral decubitus view showed a shift of the air-fluid level; (2) a cystic structure, irregular in outline, measuring up to 4 cm. in greatest diameter on posteroanterior and lateral laminagraphy. This appeared to lie within the superior segment of the right lower lobe; (3) the obstructive air-trapping phenomenon of pulmonary emphysema on expiration roentgenograms. The adjacent right lower lobe and right middle lobe were compressed and the mediastinum was shifted to the left. This was best seen on the bronchograms; and (4) apparent filling of all segmental bronchi, but with no flow of the contrast medium to the emphysematous parenchymal area on bronchograms.

The normal filling with contrast material of all segmental bronchi indicated that the bronchial cystic architectural alteration had occurred in a bronchial subdivision distal to a segmental bronchus. The apparently normal bronchogram, showing all segmental bronchi, is not a true indication of a completely normal bronchial tree, since alterations of architecture of the bronchi beyond the tertiary bronchi are difficult to discern.

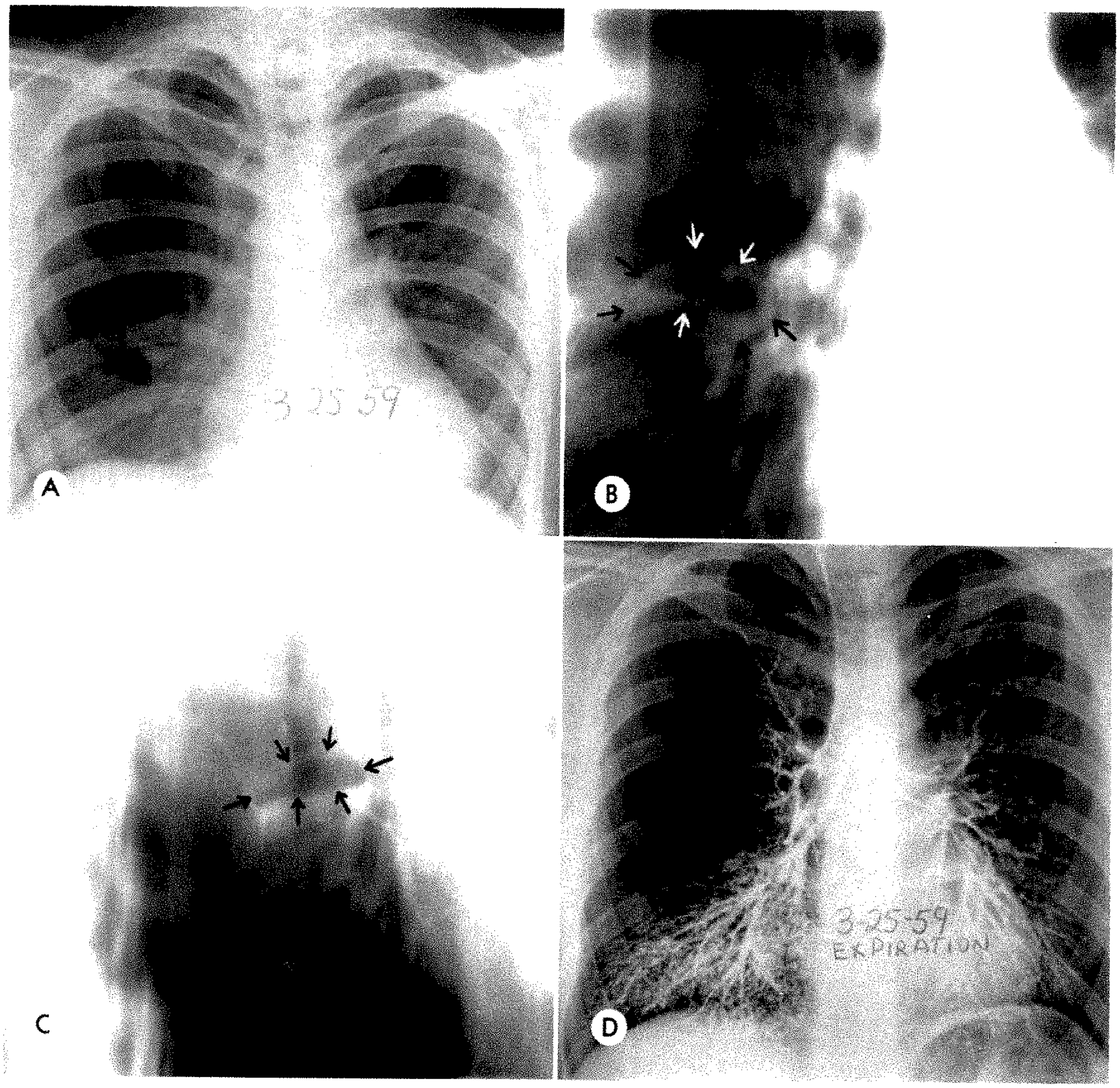

Fig. 7. Case II. (A) The cystic structure showing a fluid meniscus is seen lying medial to an area of localized emphysema. (B) Posteroanterior and (C) lateral laminagrams further demonstrate the cystic structure lying within the area of emphysema. (D) Bronchogram made during expiration clearly shows the air-trapping phenomenon of the area of emphysema.

Again in this patient, an anomalous obstructive bronchial deformity resulted in collateral aeration followed by emphysematous changes of the lung parenchyma.

DISCUSSION

The experimental findings in the dog whose chest wall had been opened and whose lung was no longer subjected to the intrapleural pressures of the respiratory cycle cannot be applied wholly to the human lung lying within an intact thorax. However, pressure differentials between the obstructed and the nonobstructed segments in the lobe exposed to atmospheric pressure roughly parallel those of the segments within the intact thorax.

By applying a broad interpretation to these pressure measurements in the experimental animal in conjunction with our specific pathologic findings in clinical cases, we have evolved the following concept of the pathogenesis of emphysema in association with segmental bronchial occlusion. Segments with obstructed bronchi will remain collapsed with endobronchial pres-

sures of ordinary respiration. When endobronchial pressure is elevated to the range of 40 cm. of water pressure (as it so readily is in straining or coughing[1]), the obstructed segments become aerated through collateral channels from contiguous normal segments with patent bronchi. Once these segments are aerated, the subsequent escape of air from them is inhibited by the check-valve mechanism at the collateral channels. Over the years the segments aerated through collateral channels become increasingly distended and ultimately true obstructive emphysema occurs.

Aeration, rather than collapse of lung tissue beyond the point of segmental bronchial obstruction, depends on continued collateral ventilation. However, collateral channel air drift may be impeded by the following factors:[1] (1) insufficient pressure differential between the segments with patent bronchi and those with obstructed bronchi; (2) accumulation of bronchial secretions distal to the point of bronchial obstruction and retrograde filling of the alveoli with these secretions; and (3) inflammatory exudate and inflammatory tissue organization in the lung tissue. Under these conditions, continued aeration is not possible, since the "wet lung" or the "organized lung" will obviously not permit continued collateral respiration. Consequently, collapse of the lung tissue often follows segmental bronchial obstruction.

SUMMARY

An experimental demonstration of collateral respiration and aeration of lung segments in which the bronchi were obstructed is presented. Clinical cases showing emphysema of such segments caused by the abnormal mechanics of chronic collateral respiration are reported.

When localized areas of emphysema or hyperaeration are found, the basic etiologic factor of segmental or subsegmental bronchial obstruction or obliteration should be sought. Then the role of collateral respiration in the pathogenesis of regional emphysema or hyperaeration will be recognized and understood.

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IDIOPATHIC UNILATERAL HYPERLUCENT LUNG*

REPORT OF A CASE COMPLICATED BY PNEUMONIA

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ONCE described and recorded in the literature, newly recognized syndromes are usually immediately discovered in increasing numbers.[2] So it will probably be with idiopathic unilateral hyperlucent lung which has also been termed the "lazy lung."[1]

It is intended here to report one additional case which, I believe, demonstrates to good advantage the classic roentgenologic signs described by Margolin *et al.*[3]

REPORT OF A CASE

N.B., a twenty-nine year old white female, was referred for a routine chest roentgenogram in February, 1959. This revealed abnormal radiolucency of the entire left lung due to a marked decrease in the vascular pattern on this side (Fig. 1). There was no evidence of overexpansion on the left and it was the initial impression that this represented absence or hypoplasia of the left pulmonary artery. The patient was subsequently hospitalized for further diagnostic studies.

Past history revealed a "double pneumonia" at the age of two years of such severity that her physician did not expect her to recover. Until about the age of ten years, the patient had a persistent "wet cough" with an apparent predisposition to numerous respiratory infections. Since that time, however, she has been asymptomatic and in excellent health. There has been no dyspnea associated with ordinary exertion or hemoptysis at any time. The chest roentgenograms of her two living children were normal. The family history was noncontributory.

Physical examination disclosed a quite healthy appearing young white female. All vital signs were normal. There was no difference observed in the expansion of the two sides of the thoracic cage. The only positive physical finding was the presence of loud, medium dry rales occurring at the terminal portion of inspiration over the entire left hemithorax, which persisted following coughing. On direct questioning, the patient recalled several physicians in the past commenting on the auscultatory finding of adventitious sounds in her left chest. Routine laboratory work was within normal limits.

Fluoroscopy during respiration revealed some restriction of the left hemidiaphragm with no significant mediastinal shift. The left hilus was quite small and normal pulsations of the hilar vessels were not observed. The most striking finding was a constant density of the entire left lung field with failure to "cloud up" normally on expiration (Fig. 2).

Pulmonary angiography was performed by injecting 30 cc. of 90 per cent hypaque with a No. 13 needle into an antecubital vein. The

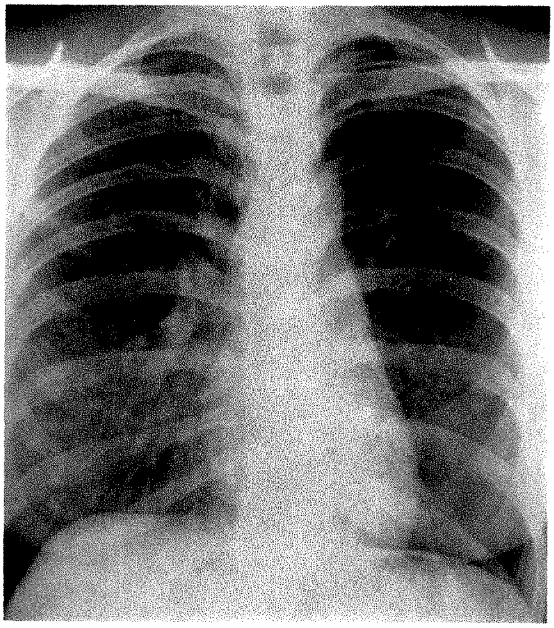

Fig. 1. Routine chest roentgenogram taken during inspiration reveals increased radiolucency of the entire left lung, apparently due to a decrease of vascular shadows, with no evidence of overexpansion.

* This paper represents the personal viewpoint of the author and is not to be construed as a statement of official Air Force policy.

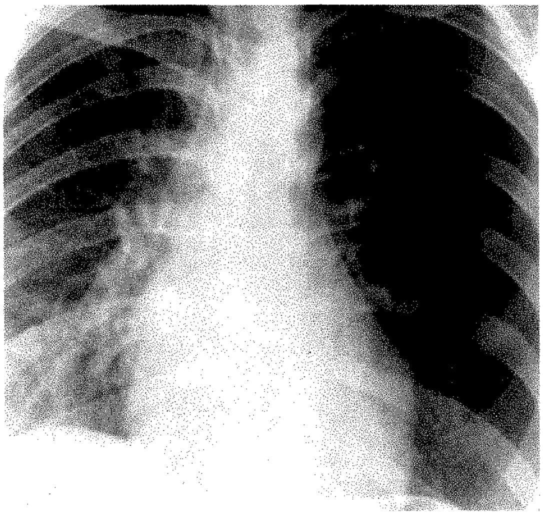

Fig. 2. Expiration roentgenogram shows normal clouding of the right lung field without increase in density on the left side. There is no significant mediastinal shift.

angiogram demonstrated a marked diminution of the pulmonary circulation on the left side (Fig. 3). Bronchography revealed a normal anatomic pattern of the major and minor bronchi bilaterally, but on the left side an unusual type of terminal bronchiectasis or clubbing was demonstrated with no alveolar filling even on a delayed roentgenogram (Fig. 4 and 5).

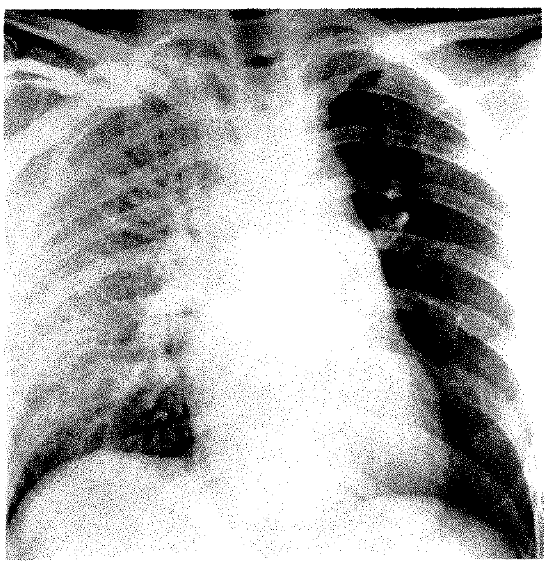

Fig. 3. Pulmonary angiogram proves the presence of a hypoplastic left pulmonary artery with normal or increased circulation to the right lung.

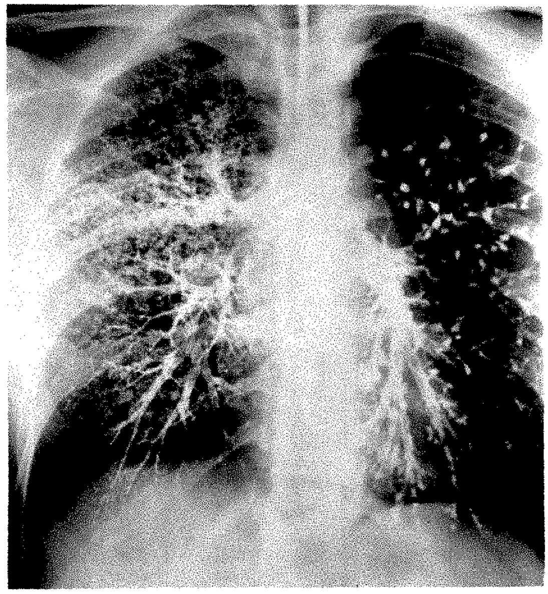

Fig. 4. Bronchogram demonstrates the terminal "club type" of bronchiectasis on the left side with normal patency and arrangement of the major bronchi. Note absence of alveolar filling. The right side is normal.

Approximately four months following the above procedures, the patient was admitted to the hospital with clinical symptoms and signs

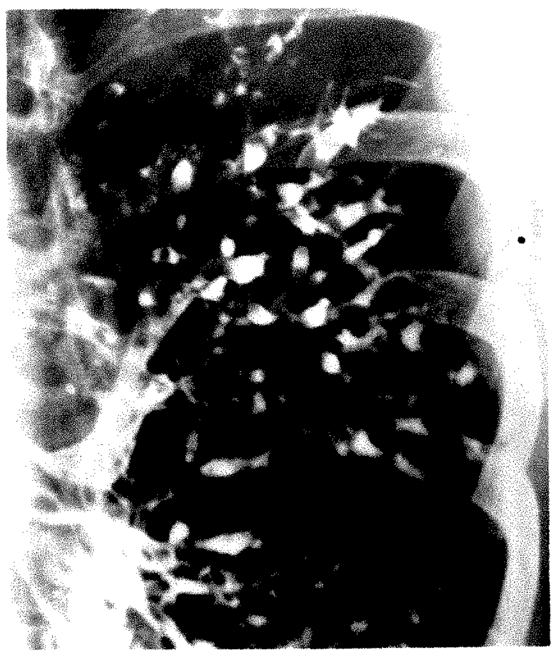

Fig. 5. Oblique bronchogram of the left upper lobe area shows the terminal clubbing in detail.

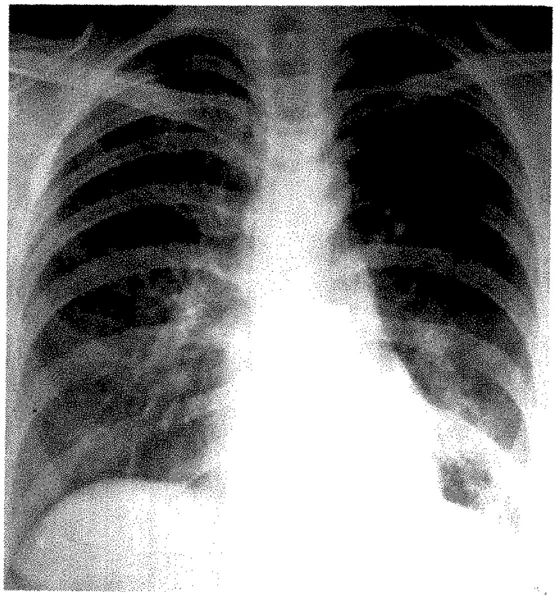

FIG. 6. Posteroanterior roentgenogram shows acute left lower lobe pneumonia, which developed four months following the above procedures and cleared rapidly on antibiotic therapy leaving no residual.

of an acute left lower lobe pneumonia. Roentgenography at that time revealed a typical pneumonic infiltration in the left lower lobe (Fig. 6) which cleared rapidly on antibiotic therapy, leaving no change in the appearance of the follow-up chest roentgenogram from the original (Fig. 1). This was the first recorded pulmonary infection since childhood.

DISCUSSION

The aforementioned changes, consisting of (1) increased radiolucency of an entire lung or lobe, with a constant normal volume during inspiration and expiration; (2) a small hilar shadow with diminution in pulmonary vascularity proved by pulmonary angiography, and (3) the peculiar terminal bronchiectatic pattern with lack of alveolar filling but with normal patency and distribution of the major and minor bronchi, characterize the roentgenologic syndrome of idiopathic unilateral hyperlucent lung.

Many of the patients previously reported with this syndrome[2] have had varying degrees of respiratory difficulty. The present case history is not one of recurrent pulmonary infections or of pulmonary symptomatology and, in fact, only one severe respiratory illness had occurred at the time of her original workup.

The etiology is not definitely known, but if the vascular abnormality is congenital, the possibility that the bronchiectasis may be acquired is suggested in the present case by the rather severe bout of pneumonia in childhood which may have resulted in permanent changes on the hypovascularized side.

SUMMARY

An additional case demonstrating classic roentgenographic, fluoroscopic, and bronchopulmonary changes of the idiopathic unilateral hyperlucent lung syndrome and complicated by an acute pneumonia on the abnormal side is reported.

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ROENTGENOLOGIC ASPECTS OF ASBESTOSIS*

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THE roentgenologic features of asbestosis have been described from time to time during the past few decades. However, the literature on the subject is still rather scanty and often misleading. Here in South Africa, where the production of a considerable proportion of the world's asbestos has been going on since approximately 1893, we have had the opportunity, particularly in more recent years, of examining large groups of workers from specific areas, notably from the Kuruman and Lydenburg districts. A study of the evolution of roentgen manifestations in individual cases, as in silicosis, has not yet been possible. Regular initial and periodic examinations have been instituted only lately. Careful correlation with necropsy findings, in contrast to the work which has been done on gold miners' silicosis, has been confined to relatively few cases. Likewise, correlation with the results of clinical and physiologic investigation has been limited.

EARLY ASBESTOSIS

It has been suggested repeatedly that a negative period exists when the disease may be present to a significant degree clinically, without being manifest roentgenologically. Judging by the very limited biopsy and pathologic material available to date, there certainly appears to be some evidence in support of this contention. This obviously has a bearing on the important and very difficult problem of the diagnosis of asbestosis in its early stage. The limits of the normal and abnormal are far more difficult to define in early asbestosis than in early silicosis, even when there is an adequate history of exposure.

Factors such as an indifferent roentgenographic technique, obesity, poor film quality, or exposure of the film during insufficient inspiration all contribute to misleading results. Roentgenography in multiple projections of the chest and specialized techniques, including macroroentgenography, are not likely to be of much help. At present, a pre-employment examination followed by a series of periodic examinations, utilizing a standardized and comparable roentgenographic technique, has the most to offer in solving the problem of making an early roentgenologic diagnosis of asbestosis and, incidentally, of also assessing the rate of progression.

As a result of observations in many individuals who have long records of service in asbestos mines and mills, it has been possible to draw up a rough classification of the more definitive roentgenographic changes that are found. These may be divided broadly into pleural changes and parenchymal lung changes. Frequently a combination of both occurs. The complications of asbestosis also need to be considered.

PLEURAL CHANGES

These by far outnumber the so-called diffuse lower zone fibrotic lung changes emphasized by previous workers. The pleural changes may be nonspecific in the form of uni- or bilateral, parietal or interlobar, thickenings of varying extent. Obliteration of the costophrenic sulci as well as diaphragmatic and pleuropericardial adhesions also occur, statistically, more frequently among asbestos workers than in other groups.

A localized recent basal pleuritis may be observed but not frank or copious pleural effusion. The veiling and lack of radiolucency in lung areas where pleural pathology exists evidently appears, in many cases,

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The views expressed in this paper are those of the author and are not to be construed as reflecting the policy of the Pneumoconiosis Bureau or of the Department of Mines of the Government of the Union of South Africa.

to be due mainly to pleural fibrosis, rather than to underlying pulmonary fibrosis. As a result of extensive pleural thickening, the cardiac outline and also the outline of the diaphragm are unsharply defined. When pleuritic adhesions are present, distortion and irregularity of contour in the form of "peaking" and "tenting" are noted. On fluoroscopy, restricted diaphragmatic mobility and diminished chest movement may be seen. It is well to remember, however, that in spite of the frequency with which pleural thickening *per se* is found in asbestos workers, this is also a fairly common isolated finding in the course of ordinary roentgenologic studies. Therefore, it would be highly presumptive to accept such evidence alone as being diagnostic of asbestosis, even in cases where a satisfactory occupational history is present.

However, a more specific pleural pathology has recently come to light in the form of added calcification and the deposition of typical pneumoconiotic plaques (Fig. 1, *A* and *B*). This has been noted as a regularly recurring feature in old asbestos workers with varying periods of service. Calcific plaque formation may be minimal or extensive, linear or occurring in irregular patches; it is usually bilateral and more or less symmetric. The plaques are often distributed along the parietal pleura, particularly in the middle and lower zones, but it is worth noting that extensive areas of calcification may be found along the anterior aspect and also that both the diaphragmatic and mediastinal pleura are commonly involved. The asbestotic plaques are different in appearance and in character from silicotic plaques, which, though not common, are usually seen in the upper zones, peripherally. It may also be empha-

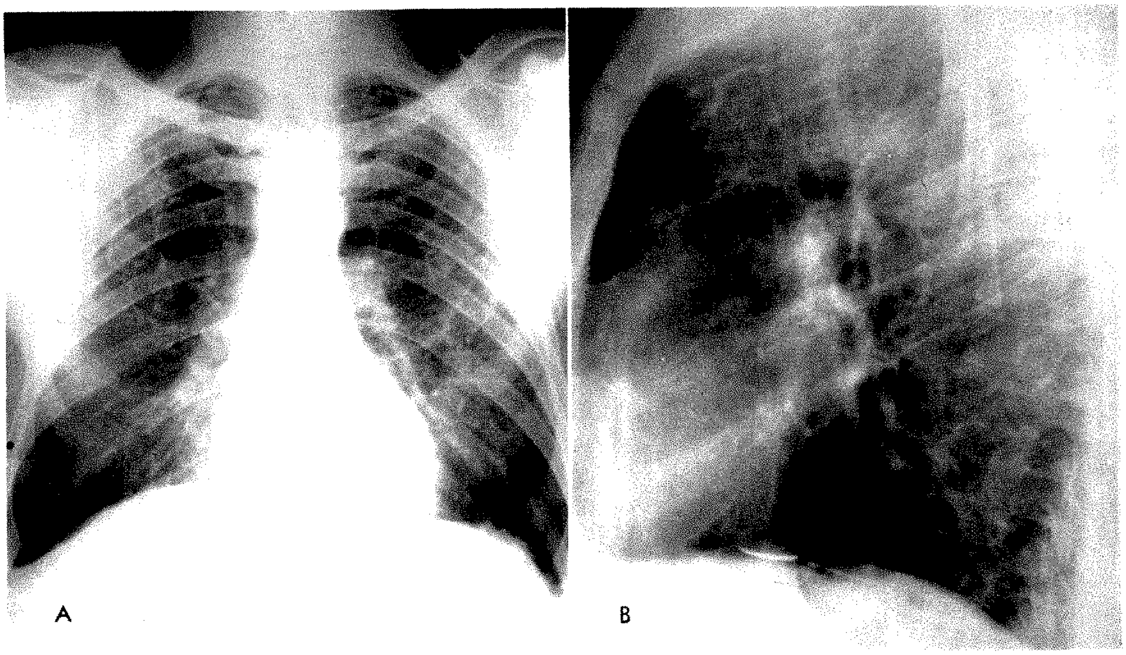

Fig. 1. (*A*) Extensive pleural plaque formation over both lung fields. Right paramediastinal and bilateral diaphragmatic plaques are also seen. (*B*) Lateral roentgenogram shows the plaques disposed along the anterior aspect of the chest and adjacent to the diaphragmatic surface.

White miner, aged fifty, with fifteen years' service as an asbestos miner in the Kuruman district, Northern Cape Province. Complained of slight dyspnea on exertion of several years' duration and pain over the right base. A cholecystectomy was performed in 1947, but no other previous major illness was present. Examination showed a well built individual, height 6'2", weight 198 pounds. The chest expansion was two and one half inches. There was no finger clubbing. Harsh breath sounds were heard. The heart was normal; blood pressure was 120/80; the electrocardiogram was normal. A Masters Effort Tolerance Test showed definite mild disability.

sized that in pure asbestosis, in contradistinction to silicosis, associated "egg shell" lymph node calcification is singularly absent. Evidently the lymphatic drainage apparatus of the lung is not implicated to the same extent in asbestosis as it is in the silicotic process following the retention of dust in the lungs.

When massive plaque formation is present, a rather characteristic bizarre pattern is produced. This is obviously different in appearance from extensive pleural calcification due to other causes, such as tuberculosis, chronic empyema and old trauma. According to recent publications, this particular pattern appears to be common to, and is diagnostic of, a group of pneumoconioses resulting from exposure to certain silicate dusts.

Smith[5] in 1952 reported a high incidence of similar calcium deposition in the pleura in a number of occupational groups exposed to various dusts, such as tremolite talc (6.3 per cent of cases); calcimine (1.7 per cent); mica (1.6 per cent); dust produced in the manufacture of bakelite insulators (1.5 per cent); and asbestos (no case). Calcium depositions were found in 35 of 8,779 subjects examined. It is noteworthy that Smith was unable to demonstrate pleural calcifications resulting from asbestos dust in the group of 261 asbestos workers. Gloyne[2] in 1938, in his classic description of the pathology of asbestosis, did mention the occurrence of "stiff, hornlike plaques." However, the first reference in the literature to asbestotic plaques demonstrated roentgenographically was made only as recently as 1955, in 1 case reported by Jacob and Bohlig. In 1956, Frost, Georg and Møller[1] of Denmark reported 11 such cases from a group of 31 insulation workers exposed for many years to mixed dust containing asbestos.

Our own experience has been that, since the registration of asbestos mines in 1953 under the 1946 Mines Act, we have seen numerous such cases, more expecially as the result of the very large surveys which have been conducted from January, 1954 to date. After constant work with silicotic beneficiaries among gold miners, the sudden presentation of significant numbers of old asbestos workers showing this new pattern of calcific plaque formation has been most striking (Fig. 2). Since then we have continued to be impressed by the fact that we seldom fail to find several such cases in every large group of roentgenograms submitted from the asbestos areas. Conversely, not a single case showing these typical plaques was ever found among all the roentgenograms of gold miners, and of the large groups mining coal, copper, iron, chrome and manganese.

LUNG CHANGES

These may be of four types:

1. As pointed out, diffuse interstitial fibrosis occurs commonly in combination with the pleural changes which have already been described (Fig. 3). The diffuse type of fibrosis found in asbestosis should

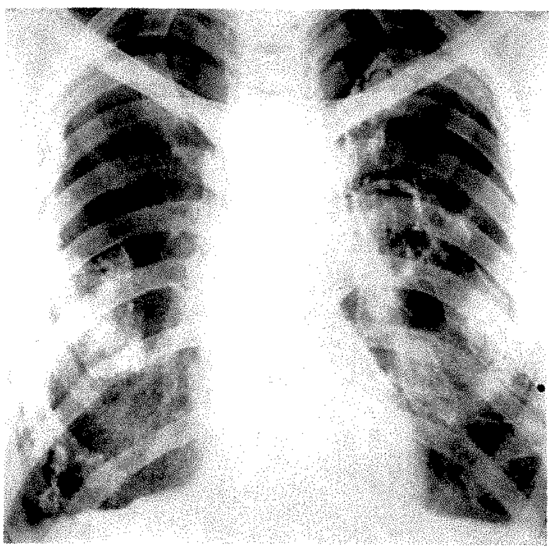

Fig. 2. Sclerotic pleurisy with extensive mediastinal, paracardiac and diaphragmatic pleural plaques.

Colored worker, aged fifty-one, with a twenty-nine year (1925–1954) history of underground asbestos mining in Northern Cape Province. He had also worked in diamond diggings in Northern Cape Province for four years (1921–1925). Examination revealed a tall, poorly nourished, weak individual, height 5′11″, weight 135 pounds, with flattened chest which had an expansion of one inch. The breath sounds were harsh and there were some marginal crepitations. The heart showed no appreciable disease; the blood pressure was 140/80. The individual was considered to be fit for light work only.

be differentiated etiologically from pulmonary collagenosis such as occurs in rare cases of silicosis, in scleroderma, rheumatoid arthritis, bilharziasis, in the general group known as "honeycomb lung," and in the so-called Hamman-Rich syndrome. Pleural thickening, which is so frequently seen in asbestosis, is not a constant accompanying feature in any of these other collagen diseases.

2. Less frequently, there are lung changes alone, presenting the classic pattern of simple uncomplicated diffuse pulmonary fibrosis (Fig. 4). This may vary in degree. There may be merely a homogeneous clouding and haze over the lung fields, particularly over the lower zones, producing a ground glass appearance. When very mild this can present great difficulty in diagnosis, especially when technical quality is questionable and when no previous roentgenograms are available for comparison. A more definite stage is one which shows a fine striated, fibrillar change in the lung structure, causing progressive reduction of pulmonary radiolucency with blurring and masking of the vascular lung markings (Fig. 5). Eventually, an advanced stage of diffuse lung induration is reached with very marked pulmonary hypoventilation which gives an unmistakable picture (Fig. 6).

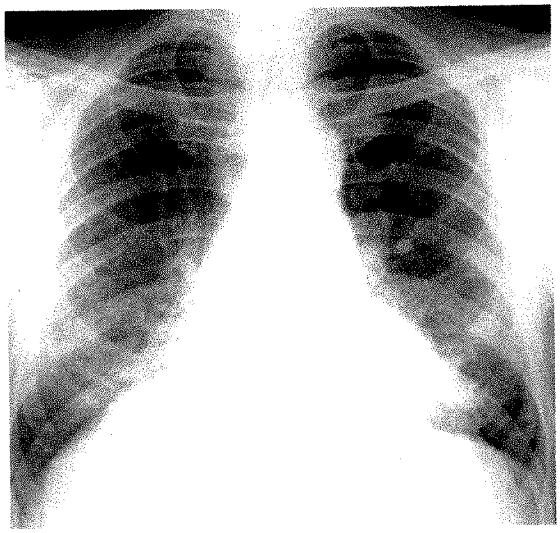

Fig. 4. Parenchymal pulmonary asbestosis with diffuse pulmonary fibrosis, which is more marked in the lower lung areas.

European, aged sixty, worked for many years in an asbestos mine in the Lydenburg district, Transvaal, both underground and on the surface in the mill. Clinically diagnosed as bronchitis with emphysema (and early cor pulmonale?).

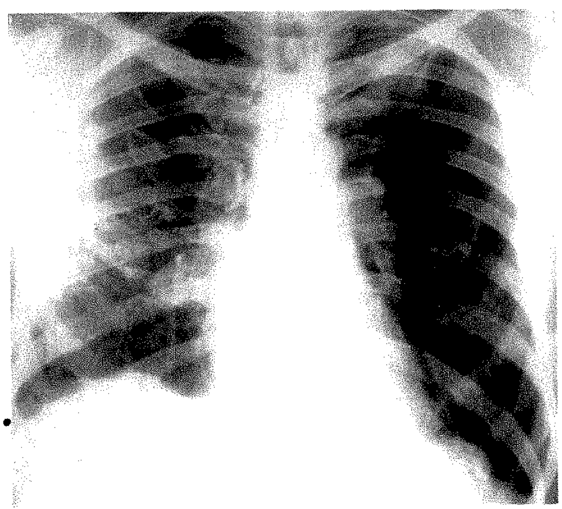

Fig. 3. Slight bilateral pulmonary fibrotic changes with dense compact pneumonic area of fibrosis in left upper lobe. The pleural thickening is particularly well marked on the right side and bilateral calcific pleural plaques are demonstrated.

Colored asbestos miner, aged forty-four, with a record of twenty-eight years' service (from 1926 on) in Cape Blue Mines. Clinically he had no complaints and apparently was a healthy individual of medium build, height 5'7", weight 143 pounds. The chest expansion was one and one half inches. Reduced resonance and distant breath sounds were noted on the right side, especially at the right lung base, with occasional crepitations. The heart was clinically normal; the blood pressure was 130/90. He was assessed fit for ordinary work.

3. Some cases present with localized areas of homogeneous, compact, pneumonic consolidation and fibrosis. These areas may occur in any part of the lung. They do not appear to be disposed in a regular lobar or segmental pattern as in the pneumonias; nor are there any accompanying infiltrative changes such as one sees in pulmonary tuberculosis. The pneumonic areas may be multiple and occasionally only one lung is involved. Associated pleural thickening is usually seen. The precise nature of these pneumonic changes is not evident and still requires further investigation. Moreover, these lung changes do not in any way re-

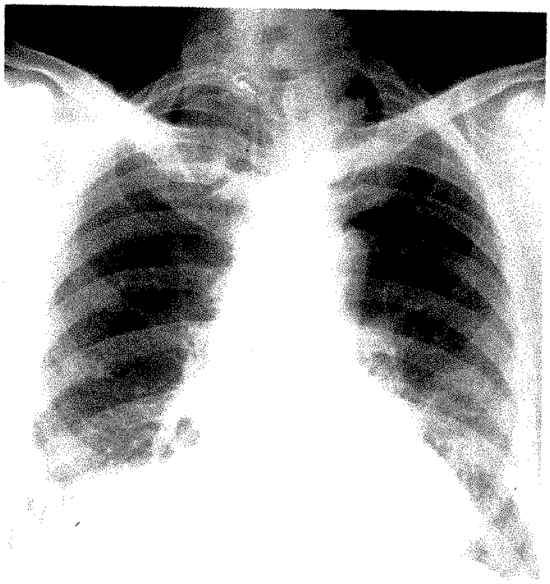

Fig. 5. Pulmonary asbestosis with diffuse lung fibrosis, particularly well marked in the middle and lower zones. The right cardiac border and the right dome of the diaphragm are unsharply defined.

Colored miner, with a history of twenty-six years of asbestos mining in Cape Blue Mines. He worked underground from 1906 on, is now a debilitated pensioner aged seventy-seven, and complains of bouts of coughing and dyspnea. Examination showed a flat chest with poor air entry and expansion of one half inch, with crepitations at the lung bases.

semble the progressive massive fibrosis which occurs in complicated silicosis and in coal workers' pneumoconiosis.

4. Due presumably to associated silica exposure, a well-marked nodular lung pattern is occasionally encountered in asbestos workers (Fig. 7). The picture may be indistinguishable from silicosis. On the other hand, a number of cases show stigmata of both asbestosis and silicosis in the form of generalized fibrosis accompanied by nodule formation. It is significant that among this group there were also several cases which exhibited fairly extensive lymph node calcification such as one sees among old silicotics. Thus far, we have observed these features which are indicative of silicosis only among workers from the Cape Blue area, where a high percentage of silica and iron has been reported in the mined asbestos.

COMPLICATIONS

The frequency of the various intrathoracic complications, which are encountered in some of the pneumoconioses, has not yet been accurately assessed in asbestosis. Pulmonary tuberculous lesions evidently occur as frequently among asbestos workers of all races as in the gold miners. A variety of forms of pulmonary tuberculosis has been observed, including extensive and frankly active lesions with cavity formation and even with disseminated miliary infiltration. While lung cancer has so far been extremely rare in our series, pleural malignancy in the form of mesothelioma has been

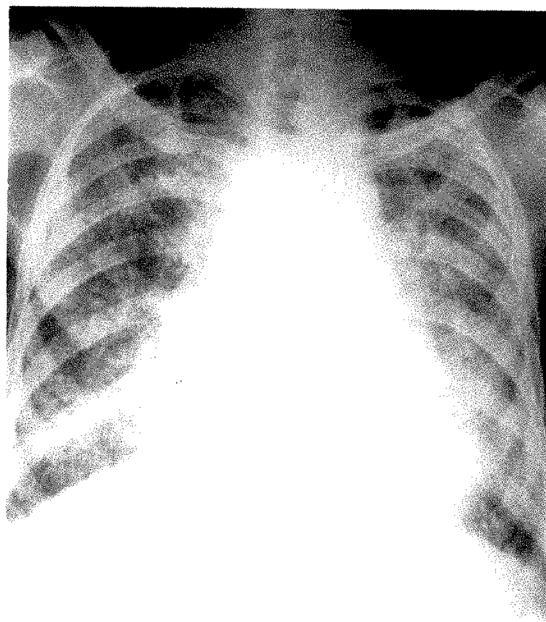

Fig. 6. Advanced asbestosis with intense fibrosis throughout both lung fields. An element of nodular fibrosis is also evident, presumably due to associated silica exposure. The heart shadow is enlarged.

Colored miner, aged fifty-four, worked from 1916 to 1954 in Cape Blue Mines, Prieska district. Of these thirty-eight years of mining, twenty-seven years were spent underground. (He holds a blasting certificate issued in 1920 and valid for asbestos mining in Cape Province only.) Symptoms of cough and shortness of breath were present for the past ten years. Examination showed poor physique, height 5′6 1/2″, weight 135 pounds, obviously dyspneic with crepitations all over the chest but mostly at the bases. Repeated sputum tests were negative for tuberculosis. He was considered fit for very light work only.

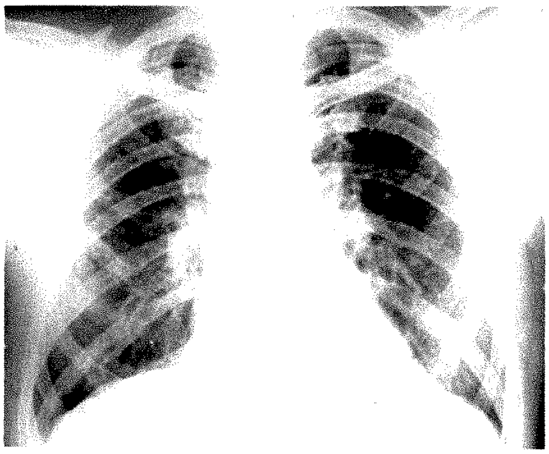

Fig. 7. Widespread nodulation in the lung fields, indistinguishable from classic silicosis. Note small bilateral diaphragmatic pleural plaques.

This patient had a history of many years' service as an asbestos miner in the Griqualand West district, Cape Province.

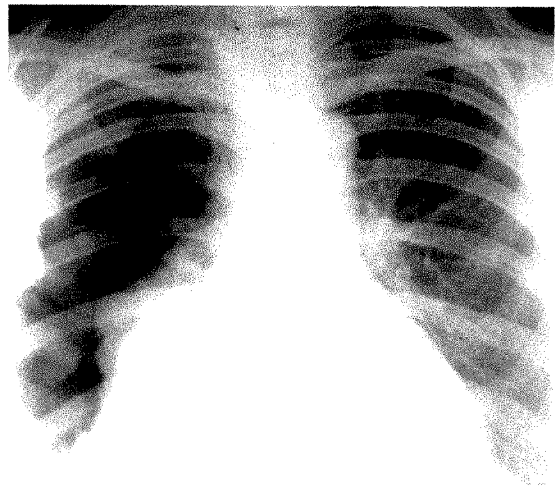

Fig. 8. Pleural mesothelioma, with induced right-sided pneumothorax. Diffuse pleural thickening and numerous rounded, nodular tumor masses on the parietal pleura and also on the visceral pleura overlying the collapsed right lung are demonstrated. Only secondary pulmonary hyperemia is evident in the left lung with no frank signs of pulmonary asbestosis.

This patient had a previous history of exposure to asbestos dust in the Kuruman district, Northern Cape Province.

relatively frequent in individuals exposed to asbestos dust (Fig. 8).

SUMMARY

1. The roentgenologic features of asbestosis as seen among asbestos workers in South Africa are described and discussed.

2. Emphasis is placed on the pleural changes, which are found more frequently than the classic diffuse pulmonary fibrosis. Pleural involvement also occurs frequently in association with lung fibrosis.

3. A characteristic pattern of sclerotic pleurisy presenting in the form of calcific pleural plaques is described. Although this pattern may be seen in a number of pneumoconioses resulting from exposure to certain silicate dusts, its incidence in asbestosis has hitherto received scant attention in previous publications.

4. The complications of asbestosis are briefly referred to, including pleural mesothelioma, which appears to be relatively common among asbestos workers in the northern Cape Province of South Africa.

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DIATOMITE PNEUMOCONIOSIS: ROENTGEN CHARACTERISTICS AND CLASSIFICATION

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THE purpose of this report is to describe certain roentgenographic aspects of pneumoconiosis seen in diatomite workers and to propose a roentgenographic classification of these changes. It is based on a review of the chest roentgenograms of 869 workers in five plants who participated in the survey conducted by the United States Public Health Service in 1953 in cooperation with the California, Nevada and Oregon State Departments of Health. A comprehensive and detailed report of this study is found in United States Public Health Service Publication 601, 1958[4] entitled "Pneumoconiosis in Diatomite Mining and Processing."

Detailed environmental studies were made to determine the extent and nature of the dust exposure. The medical studies of the employees in the five participating plants included occupational and medical histories, physical examination, roentgenograms of the chest, electrocardiograms, hematologic and urinary examinations, intradermal skin tests with tuberculin, histoplasmin and coccidioidin and pulmonary function tests. When indicated, bacteriologic studies for tuberculosis were performed. The follow-up studies included biennial chest roentgenograms on the workers in the plants and those with over two years of employment who had left the industry.

Diatomite pneumoconiosis is a relatively uncommon pulmonary condition resulting from protracted inhalation of certain forms of diatomaceous earth. Although diatomaceous earth has been known and used for approximately 2,000 years, its disease-producing propensities were first reported in the medical literature by Legge and Rosencrantz[6] in 1932. However, it was not until 1946 that it was acknowledged that exposure to certain forms of diatomaceous earth dust could result in a disabling and sometimes fatal disease.[1]

Diatomaceous earth—a light, porous substances of white, yellowish or gray color—is the fossilized skeletal remains of microscopic, aquatic, single-cell plants (algae). It is synonymous with diatomite, Kieselguhr, tripolite, infusorial earth, fossil flour and fossil silicon. In its crude state diatomite contains about 85 per cent amorphous silicon dioxide by weight.

The industrial mining of this substance dates back to 1860 in Europe (Hanover, Germany, and North Ireland) and it has been mined for approximately sixty years on the North American continent. California, Nevada, Oregon and Washington contain nearly all the commercially exploited deposits in the United States. There are about 1,000 employees engaged in diatomite mining and milling industries in these western states of whom about 800 are in California.

The diatomite-producing industry in the United States is a relatively small one. Five plants employing approximately 1,000 persons produce practically all of the diatomite in this country. However, the production of diatomite by no means represents the only method of exposure to this material. It is shipped in great quantities to all parts of the world and is used in a very wide variety of technologic processes. It plays an important part in the sugar industry, in the filtration of unfermented fruit juices, syrups, wine, beer, dry cleaning

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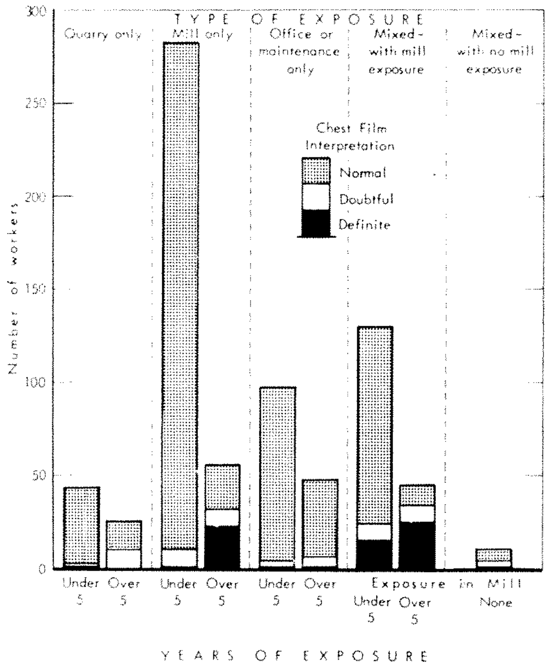

FIG. 1. Interpretations of chest roentgenograms according to type and duration of exposure.

solvents, water for drinking purposes, swimming pools, etc. It is used as a filler in paints, varnishes and lacquers in addition to the manufacture of special types of paper. It aids in the manufacture of insecticides, metal, glass and automobile polishes, detergents, plastics, concrete, matches and many other products. Its low heat-conducting properties lead to widespread use in insulation for boilers, stills, furnaces, kilns, and petroleum-cracking furnaces. In the chemical field it finds use as a catalyst.

Multiple processing techniques, including drying diatomite at temperatures ranging from 300°F. to 800°F., convert the crude diatomaceous earth to the "natural" powder. In addition to "natural" diatomite, two other forms are manufactured—calcined and flux-calcined. Straight calcining is done in a rotary kiln at temperatures ranging from 1,600 to 2,000°F. In low-temperature calcining little, if any, of the amorphous silica is converted to cristobalite, a crystalline form of silica; but as much as 20 to 30 per cent may be converted in high-temperature calcining. Flux-calcining consists of mixing the purified "crude" with a flux, usually sodium carbonate, and passing this mixture through a rotary kiln at 2,000° F. Approximately 40 to 60 per cent of the amorphous silica may be converted to cristobalite during this process along with the production of about 1 per cent tridymite, another form of crystalline silica.

The environmental studies of the survey showed that the median size of the airborne dust particles varied from 1.0 μ for straight calcined diatomite, 1.1 μ for flux-calcined material up to 2.5 μ for the crude diatomite. Median atmospheric dust concentrations in major operating areas ranged from 1 to 66 million particles per cubic foot of air (MPPCF), as determined by standard light field techniques. Five MPPCF of the cristobalite-containing product and 20 MPPCF of the crude or natural product have been suggested as the maximal concentration to which workers should be exposed.[4] Table I shows the percentage of cristobalite in the various diatomite materials.

Pathologic studies of diatomite pneumoconiosis have been reported by Nordmann[7] in 1943, Vorwald and co-workers[11] in 1949, Carnes[3] in 1954 and Caldwell[2] in 1958. These investigators concluded that protracted inhalation of diatomaceous earth produces chronic pulmonary disease in man. They are in agreement that the histopathologic changes in lung and lymph node differ in many respects from those produced by quartz.

TABLE I

WEIGHT PERCENTAGE OF CRISTOBALITE IN PARENT MATERIAL, SETTLED DUST, AND AIRBORNE DUST, ACCORDING TO PRODUCT

(5 Plants Combined)

Product	Parent Material	Settled Dust	Airborne Dust
Natural	0–1	Less than 1	Less than 5
Straight-calcined	15–21	27–52	17–22
Flux-calcined	49–61	38–75	32
All types (mixed)	—	25	16

The pathologic findings in 27 workers studied by Carnes[3] indicated that these cases fell into two groups corresponding to the simple and confluent forms. In simple pneumoconiosis the histopathologic changes consisted of "accumulation of dust cells in the alveoli, in the interstitial tissue of the lung, including the alveolar walls, and in the hilar lymph nodes with either no fibrosis or in the long-standing cases a very delicate reticular fibrosis." Conspicuous by their absence were "the cardinal features of typical silicosis; namely, the focal, discrete hyalin nodules and the whorled pattern of collagenous fibers."

In those individuals with the confluent form, there was "in addition to the foregoing changes more or less massive confluence of the lesion in the upper one-third of the lungs, with necrosis and marked fibrosis." In at least 4 of the 6 cases of the latter type, the patient's demise was attributed to the pneumoconiosis. Carnes drew no conclusions as to the role, if any, of infection in the production of these coalescent lesions. Varying degrees of focal emphysema were associated with the diatomite lesion, the lesion proper having a stellate appearance and the "focal emphysema associated with the focal dust reaction recalls the lesions in the lungs of the Welsh coal miners reported by Gough and others. However, none of these cases have shown the advanced degree of focal emphysema described in the coal miners."

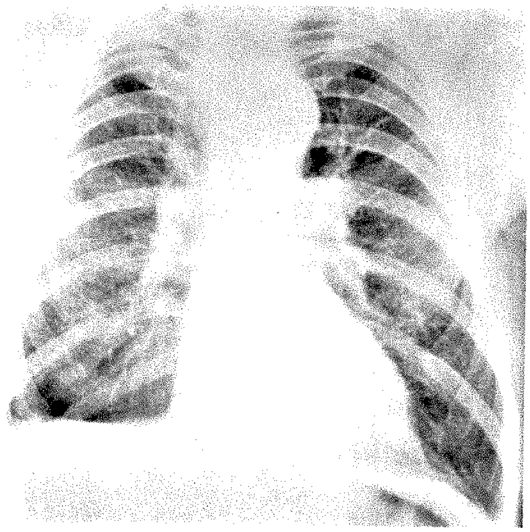

Fig. 3. LN$_3$. Profuse granular densities rather evenly distributed throughout both lungs.

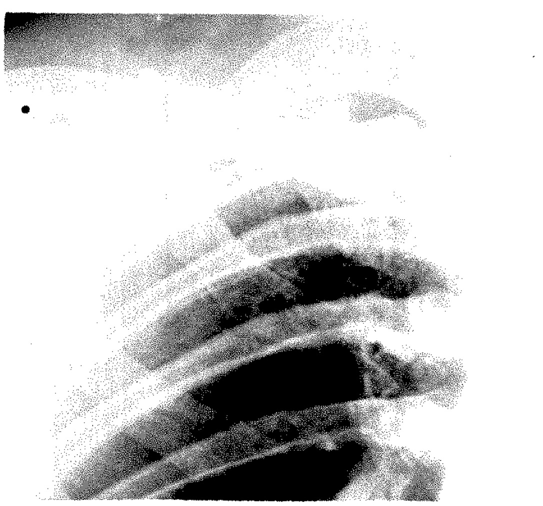

Fig. 2. LN$_2$. Fine nodular and linear deposits in both lungs above the level of the third rib anteriorly. Changes such as this may easily be mistaken for tuberculosis.

Caldwell[2] concluded that diatomite pneumoconiosis in tuberculin negative individuals follows a different pathologic and roentgenographic pattern from that in tuberculin positive individuals. However, it should be noted that the number of cases reviewed in each group was small and of doubtful statistical significance.

ROENTGENOGRAPHIC STUDY

Stereoscopic 14×17 inch chest roentgenograms of 869 employees (94 per cent of the total number of employees in the five plants) were obtained. Roentgenograms of unacceptable quality were eliminated. The chest roentgenograms were inspected initially by the physician members of the field team for quality control and for detection of abnormalities requiring the immediate notification of the employee's private physician.

Prior to the interpretation of these roentgenograms, the authors reviewed a number of proved cases of diatomite pneumoconiosis and compared the pathologic and roentgenologic changes. It was agreed that the roentgenologic changes fell into two major categories. One consisted of fine

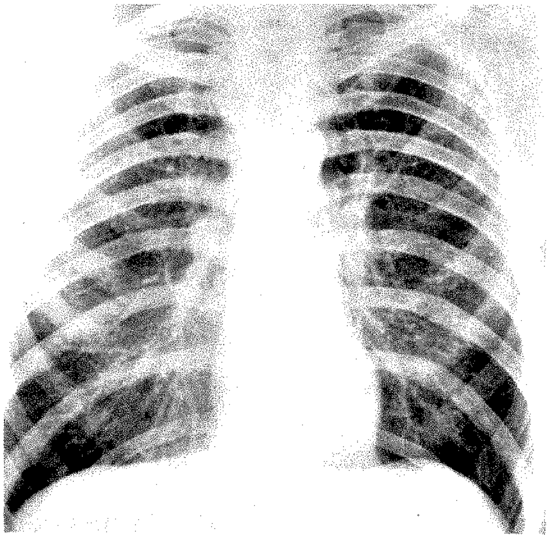

FIG. 4. LN_3. Combined linear and small nodular deposits diffusely scattered throughout both lungs.

linear and/or minute nodular shadows and the other consisted of similar shadows accompanied by larger confluent opacities.

A tentative classification was adopted. This was based upon certain features of the classifications proposed by United States Public Health Service in 1935,[8] Pneumoconiosis Research Unit in 1948,[5] International Labor Organization in 1950,[9] and Smart and Anderson in 1952.[10] Utilizing the technique suggested by Yerushalmy and co-workers[12] to test the applicability of this proposed classification, the 869 pairs of roentgenograms were interpreted independently by each of the radiologists without benefit of any clinical information. Subsequently, in conference, the radiology panel reviewed: (1) all cases in which a difference of classification was recorded by any of the interpreters, and (2) approximately 100 chest roentgenograms which had been interpreted as "normal" by all of the observers. The initial interpretations of the above cases were not known to any of the panel during the review conference. If unanimity of interpretation was not agreed upon, each dissent was recorded. Two subsequent roentgenographic interpretations and review conferences were conducted in a like manner at several month intervals.

In the initial classification of the roentgenograms, an attempt was made to differentially quantitate both the abnormal linear or reticular deposits and the nodular opacities in an area of pulmonary involvement. From the comparisons of the several successive interpretations, it became apparent that the differentiation of the two is often impossible and that the changes are usually coexistent. In the final classification, therefore, linear and nodular manifestations were combined into one category. It may be argued that this arbitrary single category of "linear-nodular" is an oversimplification. However, statistical analyses revealed great intraobserver and interobserver error in interpretations in which linear and nodular changes were classified separately. The formulation of a classification for the coalescent states of the disease presented somewhat less of a problem.

It was also found necessary to include categories to indicate the questionable existence of both linear-nodular and confluent changes. Some of the linear-nodular shadows were particularly difficult to interpret. The roentgenographic pattern and the density of these shadows are such that in some individuals, particularly the obese, it was difficult, if not impossible, to decide whether the chest roentgenogram was "normal" or showed fine but widespread

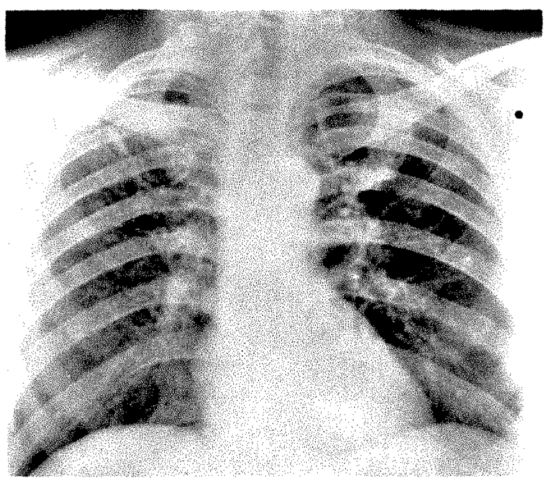

FIG. 5. LN_3 C_2. Scattered linear and nodular deposits in the upper halves of both lungs with a small confluent lesion in the right first anterior interspace.

simple pneumoconiosis. Another source of error was the differentiation between early confluent change of diatomite pneumoconiosis and tuberculosis. These problems cannot be overemphasized, and point to the great need for consistently high quality roentgenograms, experienced radiologists and multiple interpretations.

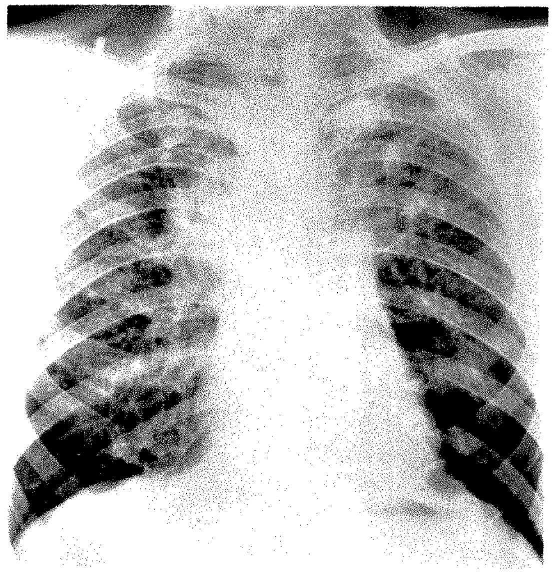

Fig. 7. LN_3 C_4. Profuse linear changes as well as scattered nodules in both lungs with a large confluent mass adjacent to the right superior mediastinum, early confluence of the left upper lobe, emphysema at the left base and marked hilar distortion.

CLASSIFICATION

The classification was based upon the total *area* of pulmonary involvement by linear-nodular densities and/or conglomerate fibrosis. After careful consideration it was decided not to classify either nodule size or concentration.

The letters "LN" were used to denote linear and/or nodular changes since consistent differentiation between these changes in the simple phase of the disease could not be accomplished. The letter "C" was used to indicate conglomerate or coalescent fibrosis. The complete proposed classification follows.

LN_1 The pulmonary structure pattern is suggestive of linear-nodular changes beyond what is considered normal or average for the given age.

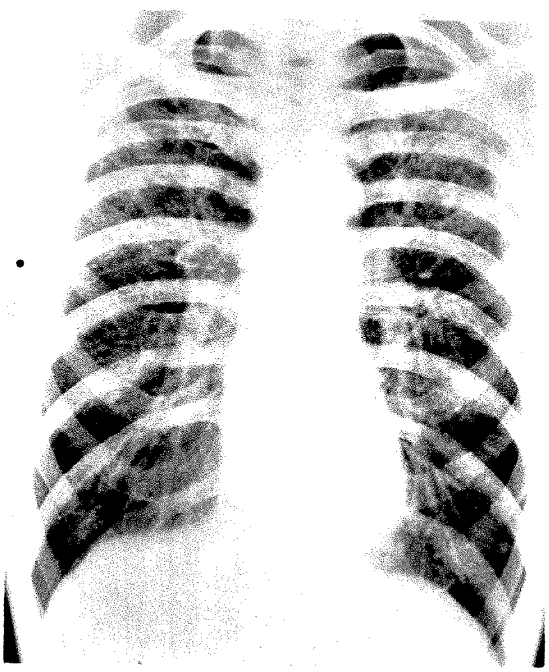

Fig. 6. LN_3 C_3. Numerous nodular and linear densities throughout most of both lungs with early confluence in both upper lobes.

LN_2 Definite abnormal linear-nodular changes extending over an area equivalent to one lung field or less.

LN_3 Definite abnormal linear-nodular changes extending over an area equivalent to more than one lung field.

C_1 Suggestive confluent opacities, superimposed on definite linear-nodular changes.

C_2 Definite confluent opacities, superimposed on definite linear-nodular densities, extending over a total area less than the equivalent of three anterior rib interspaces.

C_3 Definite confluent opacties extending over a total area, the equivalent of three or more anterior rib interspaces but not greater than the equivalent of one hemithorax. A minor degree of mediastinal and hilar distortion may be present.

C_4 Massive confluent opacities over an area greater than the equivalent of one hemithorax, or with gross distortion of the hili, heart, trachea or diaphragm.

ROENTGENOGRAPHIC CHARACTERISTICS

Diatomite pneumoconiosis is characterized roentgenographically by fine linear and/or minute nodular shadows, either or both of which may be accompanied by conglomerate fibrosis. The earliest stage of the uncomplicated form of the disease is more frequently visible in the superior halves of both lung fields below the levels of the clavicles. Most commonly, both linear and nodular shadows are seen in the same involved area. Early the linear changes are virtually indistinguishable from so-called increased bronchovascular markings. The nodules in diatomite pneumoconiosis tend to remain small, only occasionally becoming more than 1–2 mm. in diameter. The simple phase of the disease progresses predominantly by an increase in the apparent number rather than the size of the nodules, often producing a fine sandpaper appearance. The nodules are of low contrast with respect to the surrounding tissue which accounts for the difficulty in demonstrating these shadows roentgenographically early in the disease. They rarely attain the density or size of the nodules often seen in quartz silicosis.

Noteworthy, by their absence, are the calcifications frequently seen in the nodules and the hilar "egg shell" calcifications of quartz silicosis. It is also of considerable interest that in none of this group was there demonstrable mediastinal or hilar lymphadenopathy.

In the early confluent stage of diatomite pneumoconiosis, the linear and nodular changes in both upper lung fields become more apparent due to (1) minimal enlargement of the densities, and (2) contraction and approximation of these densities to each other. These "infiltrations," early, present indistinct margins and are nonhomogeneous. As the process progresses, with or without continued dust exposure, the ill-defined coalescent lesions gradually enlarge into more circumscribed and homogeneous densities. The coalescent lesions predominate in the upper lobes or apices of the lower lobes of both lungs. There is no predilection for either lung. No calcifications were seen in the coalescent areas in any of our cases.

It is also of interest that lobar atelectasis can simulate the coalescent lesion. In one of the cases studied at autopsy by Carnes,[3] the so-called coalescent lesions in both upper lung fields were in fact completely atelectatic upper lobes of both lungs with complete stenosis of both major upper lobe bronchi.

As contraction of the lesions occurs, there is frequently a pseudo-clearing of the lower lung fields due primarily to compensatory emphysema rather than to true clearing of the disease process. Although pulmonary cavitation was not seen in the workers participating in this survey, several of the cases reviewed by Carnes showed both necrosis and cavitation with and without coexistent tuberculosis.

Enlargement of the coalescent masses is usually accompanied by mediastinal, hilar and diaphragmatic distortion and progressive emphysema. Pulmonary and mediastinal distortion may occur in the presence of relatively small areas of confluence. Carnes' cases revealed spontaneous pneumothorax and cor pulmonale as relatively frequent complications in the terminal phases of the disease. No instances of spontaneous pneumothorax were encountered in this study.

RESULTS OF ROENTGENOGRAPHIC INTERPRETATIONS

Of the 869 employees studied in the 1953–1954 survey (Table II), 78 workers or 9.0 per cent had doubtful evidence of pneumoconiosis. Another group of 78 individuals or 9.0 per cent had definite roentgenographic evidence of diatomite pneumoconiosis, and 32 of these (41 per cent) had confluent disease. Of the entire group of employees, 84 had incomplete medical histories and physical examinations. The percentages of positive roentgenograms was not altered significantly by the deletion of these individuals from the statistical analysis. Another group of 47 employees was

TABLE II

ROENTGENOGRAPHIC INCIDENCE OF PNEUMOCONIOSIS IN DIATOMITE WORKERS BY STUDY GROUP

Interpretation of Chest Roentgenograms	Study Group: All Workers in Study		Study Group: Workers with Complete Examination		Study Group: Workers with History of No Dust Exposure Prior to Entering Diatomite Industry	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Normal O	713	82.0	642	81.8	612	83.0
Doubtful LN_1	78	9.0	69	8.8	58	7.9
Definite:	78	9.0	74	9.4	68	9.1
Simple LN_2, LN_3	29	3.3	28	3.6	24	3.2
Simple LN_2, C_1, LN_3, C_1	17	2.0	16	2.0	16	2.1
Confluent C_2, C_3, C_4	32	3.7	30	3.8	28	3.8
Total	869	100.0	785	100.0	738	100.0

also excluded from analysis since their occupational histories indicated that prior employment had involved exposure to other dusts for a period in excess of one year. Although the abnormal roentgenograms of these individuals with prior dust exposures were not characteristic of other pneumoconioses, exclusion from the statistical analysis appeared to be indicated. Again, no significant difference in the percentage of positive roentgenograms resulted from this deletion.

The work assignments of each employee were categorized as quarry, mill, or office and maintenance. Each individual's total employment was described in terms of the approximate number of years in each type of activity. Figure 1 presents the distribution and correlation of the interpretation of the chest roentgenograms relative to the years of employment in each activity. All workers with other dust exposures and incomplete histories and physical examinations were excluded from the statistical analysis.

The major occupational hazard was in the mills. Of the employees with five years or less of employment in this activity alone, only 0.4 per cent had definite simple pneumoconiosis, and none had confluent disease. However, of those who were employed in the mills only for more than five years, 17.0 per cent had simple pneumoconiosis and 23.2 per cent had confluent disease.

In contrast, no employee with a work history of five years or less in the quarry alone had definite evidence of pneumoconiosis. However, 40 per cent of those employed in the quarry for more than five

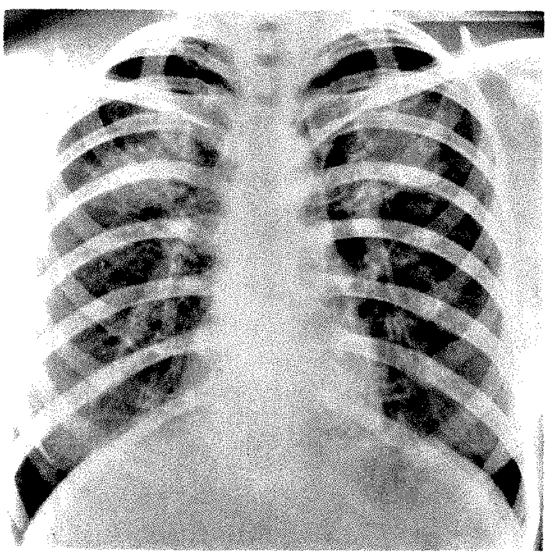

FIG. 8. LN_2 C_4. Large confluent masses bilaterally with surrounding emphysema and distortion of the hili. A few linear and nodular densities are also present.

years showed doubtful changes. No cases of confluent disease were observed in the quarry workers, irrespective of the number of years of employment in this activity.

TUBERCULOSIS

The suspected relationship between pulmonary tuberculosis and many of the silicoses suggested the need to determine whether there might be a similar relationship with diatomite pneumoconiosis; particularly since there were a number of employees who demonstrated pulmonary changes indistinguishable from the linear infiltrates commonly seen in tuberculosis. Correlative analyses were made among those employees with positive reaction to 0.0001 mg. purified protein derivative and those with roentgen evidence of diatomite pneumoconiosis, particularly those with confluent disease. The total percentage of positive reactors was 33.7 per cent. There were 43.6 per cent positive reactors among all those showing suspicious or definite roentgen evidence of pneumoconiosis and 42.9 per cent in the group with coalescent disease. These indeterminate results, coupled with the small sampling, indicate that this study produced no statistically significant evidence of the relationship between these two diseases. It is worthy of note that 57 per cent of the 28 cases with confluent pneumoconiosis had negative tuberculin reactions. These figures probably do not reflect the true prevalence of tuberculosis since some workers who developed active tuberculosis have been known to have left the industry.

SUMMARY

1. The roentgenographic changes of diatomite pneumoconiosis are described and a new classification proposed.

2. Roentgenographic examination of 869 diatomite workers showed definite changes consistent with pneumoconiosis in 78 individuals (9 per cent). Of these, 32 (41 per cent) had confluent disease. An additional 9 per cent of the employees had doubtful evidence of pneumoconiosis.

3. An interrelationship between diatomaceous earth pneumoconiosis and tuberculosis has not been established.

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PULMONARY HISTIOCYTOSIS X*

A CASE REPORT

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ALTHOUGH reports in the literature indicated a growing awareness of the fact that Schüller-Christian disease and Letterer-Siwe disease were clinical variations of the same basic process, it remained for Jaffe and Lichtenstein[9] in 1944 to add the most benign variant, eosinophilic granuloma of bone, and to demonstrate a pathologic relationship in all three disorders. Later they proposed the term "histiocytosis X" as an appropriate designation for this triology to emphasize the histiocytic proliferation common to all. Since that time numerous articles appeared dealing with the many variants seen clinically; and many etiologic hypotheses have been proposed. Among these variants is one in which the process involves the lungs to a greater or lesser extent. Some of these cases have had concomitant bone lesions, but others were distinguished by pulmonary involvement alone. Documented cases of this variant of histiocytosis X (in which pulmonary biopsy was obtained) were first recorded by Farinacci *et al.*[4] in 1951, and since that year have been reported in increasing number. The purpose of this paper is to re-emphasize the place of this entity in the differential diagnosis of miliary pulmonary infiltrations by presenting another such case.

REPORT OF A CASE

This twenty-one year old white male was admitted to the United States Naval Hospital, Charleston, South Carolina, on August 17, 1959 because of pain in the left knee due to traumatic ligamentous injury. His only other complaint was a nonproductive cough of one year's duration. He denied other cardiorespiratory symptoms as well as chills and fever. Admission chest roentgenograms (Fig. 1, *A* and *B*) revealed a widely disseminated, finely nodular

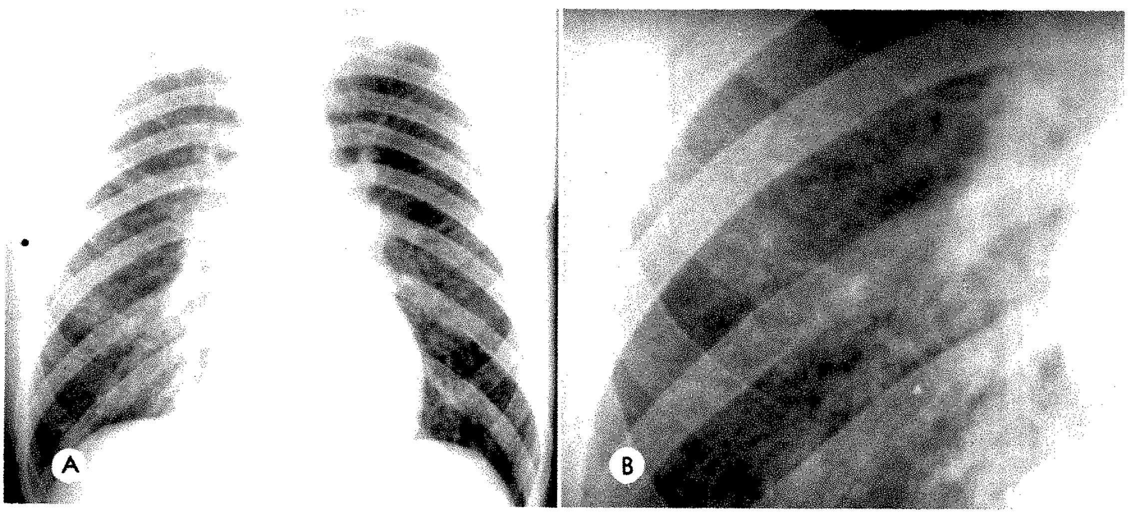

Fig. 1. (*A*) Posteroanterior roentgenogram of the chest shows a widely disseminated, finely nodular infiltration throughout both lung fields. Several small areas of confluence of the nodules are present but no frank consolidation. (*B*) A slightly magnified view of the right middle lung field demonstrates the finely reticulated background as well as the nodular infiltration.

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infiltration of both lungs. Because of these findings he was transferred to the medical service for investigation.

Physical examination revealed a young white male in no distress. There was evidence of instability of the left knee joint. The firm tip of the spleen was palpated by at least two observers; otherwise, the examination was negative. The past history was noncontributory. A chest roentgenogram taken on induction into the Air Force in January, 1957 was normal.

Laboratory studies showed the white blood cell count, hemoglobin, hematocrit, uninalysis, serology, calcium, phosphorus, albumin, globulin and alkaline phosphatase to be within normal range. A bromsulphalein test revealed 7 per cent retention in forty-five minutes. An electrocardiogram was normal. Cultures of the sputum and bronchial washings for bacterial pathogens as well as fungi and acid fast bacilli were not significant. Purified protein derivative tests #1 and #2 were negative as were skin tests with histoplasmin, coccidioidin and blastomycin. Pulmonary function tests consisting of vital capacity, timed vital capacity, and maximum breathing capacity were within normal limits. Blood gas studies were as follows: oxygen saturation at rest 84.2 per cent with an increase to 91.4 per cent after exercise and to 95.3 per cent after breathing 100 per cent oxygen for fifteen minutes. These results were interpreted to indicate a mild degree of physiologic pulmonary arteriovenous shunting and to be incompatible with an alveolocapillary block. A complete bone survey was negative. Bronchoscopy disclosed a diffuse hyperemia of the mucosa but was otherwise normal. A supraclavicular lymph node biopsy showed only reactive hyperplasia.

On October 5, 1959 an open pulmonary biopsy was performed under general anesthesia. The lung was described as grossly infiltrated with very fine 2–4 mm. nodules. The pleura was uninvolved by the process, and there was no evidence of cyst formation. A biopsy of the right lung was obtained at this time and handled under sterile technique.

The specimen measured 1 cm. in diameter and was finely nodular upon palpation. Its bisected surface showed grayish 3 mm. nodules, one of which was concisely outlined, although the others were less sharply defined (Fig. 2). One half of the specimen was emulsified with sterile broth, and aliquots of the mixture were used to inoculate blood agar, EMB agar, chocolate blood agar and thioglycollate broth. Slants of Sabouraud's agar and Petragnani's medium were also inoculated. Growth was not obtained on any of these media. The remaining half of the specimen was fixed in 10 per cent formalin and routine hematoxylin and eosin stained sections were prepared from the block. Examination of these sections disclosed focal accumulations of histiocytes and eosinophils (Fig. 3), typical of eosinophilic granuloma. In addition, there was interalveolar septal fibrosis with prominent epithelization of these thickened septa. In some areas the fibrosis was extremely marked and explained some of the nodularity noted grossly. In other foci the thickened septa outlined cystic spaces which adjoined each other in such a way as to give the impression of "honey-combing" on a microscopic scale. Within the areas of active histiocytic proliferation, the process appeared to involve the walls of the small blood vessels (Fig. 4). The total histologic picture was one of histiocytosis X, demonstrating various stages of maturation.

The patient was placed on meticorten, starting with 40 mg. daily in divided doses. This was continued for one month and then gradually decreased over another six weeks because the roentgenographic appearance remained unchanged and because Cushingoid changes were observed. The patient had no symptomatic improvement when last seen in August, 1960.

Comment. This is a rather characteristic case of pulmonary histiocytosis X. The patient is a young white male whose disease

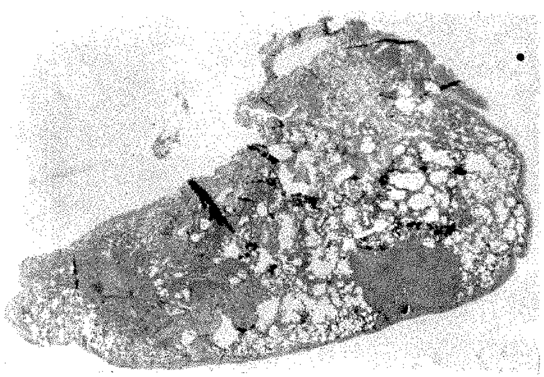

Fig. 2. Low power macrophotograph of entire tissue section. Note subpleural nodule at lower right and extensive fibrosis at left. Interalveolar septal fibrosis with emphysema can be seen above the subpleural nodule. (H. & E. ×18.)

was discovered on routine admission chest roentgenograms and whose symptomatology consists only of cough. There is no obvious explanation for the palpable spleen which has not been a common finding in other reported cases. Perhaps this indicates that the disease process is not limited to the lung. On the other hand, the failure of the spleen to continue to enlarge as well as the unchanging cough and roentgenographic findings suggest lack of progression of the process. No obvious benefit was derived from corticosteroid therapy, which adds further support to the thesis of Timmes *et al.*[11] that this form of treatment has little to offer in pulmonary histiocytosis X.

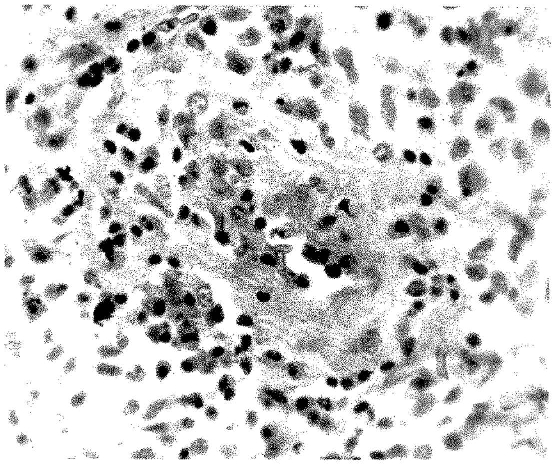

Fig. 4. Arteriolar involvement within the lesion. Note the presence of eosinophils within the vessel wall and the apparent dissolution of the latter. (H. & E. ×430.)

DISCUSSION

Pulmonary histiocytosis X may involve the lungs as part of a generalized process, as the major manifestation of a disease occurring in several different organs or as the only manifestation of the disorder. Recently, Nadeau *et al.*[8] found in the literature 21 cases with disease originating in the lungs and added 7 of their own. Not included in this review were the 6 cases of Timmes *et al.*,[11] the case of Mengis,[7] and one case of Pagan-Carlo and Haley.[9] Thus the total number of reported cases with pulmonary involvement as the sole or major manifestation of the disease, including the case herein reported, is approximately 37. It is to be expected that, as open pulmonary biopsy becomes more commonly used, many more instances of this process will be uncovered.

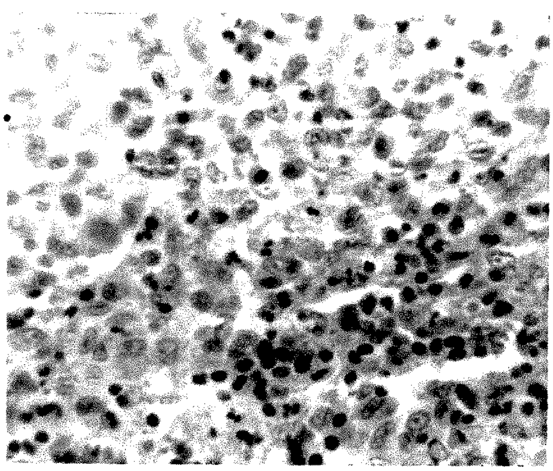

Fig. 3. Photomicrograph of subpleural nodule. Note the pale nuclei of the histiocytes at the upper left, and the dark nuclei of the eosinophils below and to the right. (H. & E. ×430.)

The disease appears to occur primarily in young and middle aged adult males. Since most of the early reports originated from military and Veterans Administration hospitals, it was assumed that the preponderance of males in these series was due mainly to the selected population; however, the report of Nadeau *et al.*,[8] originating from the Mayo Clinic, included 6 males and only 1 female, indicating that there may be a true predilection of this disorder for the male.

Symptoms are often mild and may not concern the patient, so that the diagnostic studies are usually undertaken because of an abnormal routine chest roentgenogram. However, most of the patients have complained of a dry or slightly productive cough. Dyspnea, low grade fever, weight loss, fatigue and mild constitutional symptoms are occasionally encountered.

Usually the physical examination is unrevealing and lymphadenopathy is not a feature. Examination of the chest is generally normal unless pulmonary fibrosis and emphysema have resulted or pneumothorax

is present. Rarely, wheezes and rales have been noted.

Laboratory studies are equally unrewarding. A wide variety of physical, chemical and pathologic studies have been undertaken in these patients. The white blood cell count and differential are usually normal, although mild (and probably insignificant) eosinophilia has been encountered. Albumin-globulin ratios are occasionally altered. Bronchoscopy is either normal or reveals hyperemia of the mucosa. In general, cultures of sputum, blood, gastric washings, and bronchial secretions have been noncontributory, as have skin tests for tuberculosis and the commun fungal diseases. Bone marrow, liver, and scalene lymph node biopsies have not helped in the diagnosis.

Pulmonary function studies have yielded varied results. Two of Nadeau and coworkers'[8] patients had evidence of fibrotic and obstructive disease, and one was normal. Timmes *et al.*[11] performed extensive pulmonary function studies on all 6 of their patients with pulmonary involvement. They found a slightly reduced vital capacity in 2, minimal slowing of the timed vital capacity in all, and a normal maximal breathing capacity. The commonly used spirogram was thus virtually normal in all their cases as it was in the case of Mengis.[7] On the other hand, residual volumes and the residual volume to total lung capacity ratio were elevated in all their patients, and the compliance was reduced in 4, indicating overdistention of the lungs. Blood gas studies were normal or nearly so in all of their cases.

Two distinct roentgenographic patterns have been described: (1) a generalized, disseminated, nodular, granulomatous infiltration of both lungs and (2) a reticulated background of diffuse interstitial fibrosis. The case herein recorded was no exception. The admission chest roentgenogram showed a very fine, diffuse nodularity disseminated through both lungs. Also found were a notable absence of hilar lymphadenopathy, consolidative parenchymal infiltration, and pleuritic reaction. This appearance remained unaltered during the ten month follow-up.

With more than eighty lesions producing a disseminated miliary appearance in the lungs, it seems unlikely that the radiologist would be successful in offering a specific diagnosis when confronted with the roentgenographic picture of eosinophilic granuloma of the lung. However, absence of consolidative infiltrations, acute pleuritic reactions, and cavitary disease correlated with the clinical picture of a healthy patient tends to eliminate most of the acute bacterial and mycotic processes. Careful examination of the chest roentgenogram shows the infiltration to be as closely dispersed in the apical regions as in the bases, if allowance is made for the increased pulmonary volume at this location. This tends to eliminate most, if not all, of the pneumoconioses, since they generally appear most prominent in the basilar regions of the lungs, which receive the greatest aeration. The absence of hilar lymphadenopathy, obvious lymphangitic and perivascular reaction further narrow the probabilities, tending to eliminate sarcoidosis, other granulomatous infiltrates, various malignant processes, and collagen diseases.

In the experience of others, a "honeycomb" pattern has been frequently seen. In the opinion of at least one author, the association of this "honey-comb" pattern with spontaneous pneumothorax should suggest this disease. Although such a combination was not present in our case, this diagnostic feature is worthy of note.

In the final analysis, the precise diagnosis rests upon thoracotomy with pulmonary biopsy. The histopathologic appearance is distinctive and diagnostic; it has been reviewed by Auld[2] in a report of 5 personally studied cases as well as those previously reported in the literature. In general, it includes focal accumulations of histiocytes and eosinophils, areas of fibrosis, and cystic formations. Auld draws attention to vascular changes present in these nodules; he noted fibrinoid degenera-

tion of the arteriolar walls with actual invasion of the vascular structures by histiocytes and eosinophils. He further noted the presence of emphysematous changes in the pulmonary parenchyma distant from the involved areas. It is generally believed that the active stage of the process is characterized by the cellular histiocytic nodule, and that maturation of the nodule results in, at first, interstitial fibrosis, and later a more generalized fibrosis. By-products of this fibrotic change include cyst formation which may be of such degree as to merit the term "honey-combing."

The etiology of this disorder is unknown. Although many hypotheses have been advanced, none of them have been supported by realistic confirmatory evidence. A recent approach to the problem is from the standpoint of hypersensitivity. Auld[2] cites the presence of arteriolitis and fibrinoid degeneration within the involved areas as evidence of an allergic mechanism basic to the disease. He compares the process, then, with periarteritis nodosa and Löffler's syndrome, considering all three conditions to share a basic etiology in hypersensitivity. Despite this promising clue, a great deal remains to be learned of the underlying stimuli of this disorder.

The prognosis is uncertain, although in many cases it appears to be good. Three serious complications are encountered. Because of the cyst formation which may occur, pneumothorax occasionally results and may be recurrent or even bilateral. Diabetes insipidus may appear subsequent to the discovery of the chest lesion. Finally, pulmonary fibrosis and emphysema with chronic cor pulmonale may eventuate. On the other hand, spontaneous remission is frequently encountered, as is lack of progression of signs and symptoms. Occasionally, the disease may run a fulminating course with death resulting in a short time.

There is no agreement as to treatment. In the past radiation therapy was utilized because of the response of the bony form of the disease to this form of treatment. It appears to be largely abandoned because of the lack of responsiveness and the consideration that since fibrosis may be the result of the granulomatous process it does not appear logical to apply a form of treatment which in itself may induce fibrosis. Adrenal cortical steroids are the most common current agents in use. Nadeau *et al.*[8] found 11 cases treated with steroids and state that most were improved, although only 2 completely cleared. Five of their 7 patients were given steroids. Three developed roentgenographic evidence of clearing, one was followed for only six weeks with improvement in pulmonary function, and one improved although follow-up roentgenograms were not available. Mengis'[7] patient noted improvement in symptoms before the initiation of steroid therapy, but no change in the roentgenograms was observed after nine weeks, and treatment was discontinued. Livingston's[6] case did not respond to one course of treatment and then appeared to respond to a second course given six months later. On the other hand, Timmes *et al.*[11] noted improvement in 5 of their 6 cases with no therapy whatsoever, and no response in the one case in which steroids were given. They do not believe steroid therapy is indicated unless there is evidence of continuing progression of the disease, whereas Nadeau *et al.*[8] believe that a course of steroid therapy is indicated for every patient.

We have noted no improvement in our patient who was given sufficient steroid therapy to produce changes of the Cushing type. It seems likely to us that, since evaluation of treatment is so difficult and since spontaneous remission is so common, it is unlikely that steroid treatment has really been of benefit and that the good results are frequently coincidental. Nevertheless, there is good theoretic basis for the administration of an agent which inhibits fibrosis, and so further evaluation of the steroids is indicated.

SUMMARY AND CONCLUSIONS

1. An additional case of pulmonary histiocytosis X is reported with the intent of

re-emphasizing the place of this entity in the differential diagnosis of miliary pulmonary infiltrations.

2. The case presented is a characteristic one. An admission chest roentgenogram revealed diffuse, nodular, miliary infiltration in a young white adult male in good health with a chronic cough. The diagnosis was established by pulmonary biopsy. The disease has neither progressed nor regressed despite a course of steroid therapy.

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EXCAVATING PULMONARY METASTASES*

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WHILE spontaneous cavitation of malignant primary tumors of the lung has been widely reported, it is regarded as unusual in metastatic pulmonary nodules. A search of the literature has yielded 43 cases of the latter, the majority having been reported as incidental observations or differential diagnostic problems. These cases are summarized in Table I. Examples of necrosing pulmonary lymphoblastomas have not been included since the propriety of designating these as metastatic deposits is questionable.

In most reports dealing with excavating pulmonary tumors, local circulatory inadequacy is cited as the primary cause. Usu-

TABLE I

REPORTED CASES OF ROENTGENOGRAPHICALLY DETECTED NECROTIZING PULMONARY METASTASES

Author	No. of Cases	Site of Primary Growth	Histopathology	No. of Metastases
1. Bristowe[2]	1	Pharynx	Squamous cell carcinoma	———
2. Farrell[7]	1	Undetermined	Sarcoma	Multiple
3. Dolgoff and Hansen[5]	1	Bone	Ewing's sarcoma	Multiple
4. Katzev and Bass[11]	1	Colon	Adenocarcinoma	Multiple
5. Salzman, Reid and Ogura[29]	2	a. Testes b. Pancreas	a. Seminoma b. Ductal adenocarcinoma	Multiple Multiple
6. Minor[23]	4	a. Urinary Bladder b. 3 cases with no primary stated	a. Squamous cell carcinoma b. ———	a. ——— b. ———
7. Wigh and Gilmore[37]	1	Uterine cervix	Squamous cell carcinoma	Solitary
8. Rigler[27]	1	Bone	*Osteogenic sarcoma	Multiple
9. La Foret and La Foret[13]	6	a. Mediastinum b. 5 cases, breast or pancreas	a. Teratocarcinoma b. Adenocarcinoma	a. ——— b. ———
10. Seaman and Arneson[30]	1	Uterine cervix	Squamous cell carcinoma	Solitary
11. Lichtenstein[18]	1	Bone	Osteogenic sarcoma	Multiple
12. Meyers and Sala[22]	1	Lung	Squamous cell carcinoma	Multiple
13. Wellens[36]	2	a. Lung b. Penis	Squamous cell carcinoma Squamous cell carcinoma	a. ——— b. ———
14. Deck and Sherman[4]	19	a. Urinary bladder b. Lung c. Bone d. Kidney e. 15 cases with no primary stated	a. Squamous cell carcinoma b. ——— *c. Osteogenic sarcoma *d. Wilms' tumor e. ———	a. ——— b. ——— c. Solitary d. Multiple e. ———
15. Curran and MacCarthy[3]	1	Rectum	Adenocarcinoma	Multiple
Total	43			

* Necroses detected after irradiation of nodules and/or chemotherapy.

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ally, it is postulated that necrosis results when the size of the tumor exceeds the available blood supply. Other suggested mechanisms are infarction of the regional nutritional vessels by the growing tumor or blockage of a bronchus in the same fashion with subsequent infection and abscess formation distal to the obstruction.

This report was prompted by the relative frequency of cases of excavating pulmonary metastases at M. D. Anderson Hospital and Tumor Institute, many of which were seemingly not explained by the theories noted above. A series of cases was therefore studied in an attempt to determine: (1) the roentgenographic incidence of excavating metastatic pulmonary tumors; (2) the location and histologic type of primary tumors; (3) a mode of pathogenesis; (4) the characteristic roentgenographic criteria, if any; and (5) the feasibility of identifying the site of the primary lesion by the appearance of its metastases. For these purposes, the chest roentgenograms of 6,729 consecutive patients seen between August 1, 1955 and February 1, 1957 were reviewed. Each patient had been referred with at least a tentative diagnosis of neoplastic disease and only those with unequivocal roentgenographic evidence of pulmonary metastases were selected for this study. The distribution of the metastasizing primary tumors is recorded in Table II. No attempt has been made to indicate the frequency of pulmonary metastases with respect to the various primary lesions nor does the presence of metastatic disease in the chest imply that all patients suffered from detectable metastases when first seen. Many in this series developed pulmonary metastases months or years after definitive therapy, but were included since at least one positive chest roentgenogram was made during the eighteen month period.

Initially, the roentgenographic diagnosis of a cavitating pulmonary tumor was based upon the criteria of Wigh and Gilmore:[37] (1) well circumscribed intrapulmonary mass; (2) centrally located cavity; (3) thick, easily defined wall; (4) irregular or actually nodular inner wall; (5) absence of parenchymal inflammatory change elsewhere; and (6) the presence of additional metastatic lesions (Fig. 1, *A* and *B*). How-

Table II

DISTRIBUTION OF PRIMARY TUMORS WITH PULMONARY METASTASES

Primary Site	No. of Cases	No. Necrotizing
1. *Head and Neck*		
a. Lip	3	0
b. Mouth	3	1
c. Tongue	3	0
d. Pharynx	4	2
e. Larynx	11	1
f. Thyroid	21	0
g. Parotid gland	4	0
h. Miscellaneous	5	0
	54	4
2. *Gastrointestinal Tract*		
a. Esophagus	5	0
b. Stomach	3	0
c. Colon	16	3
d. Liver	1	0
e. Pancreas	2	0
	27	3
3. *Genitourinary Tract*		
a. Kidney	15	0
b. Bladder	6	1
c. Ureters	2	0
d. Prostate	4	0
e. Corpus	7	0
f. Cervix	30	4
g. Vulva	1	1
h. Ovary	9	0
i. Testes	8	0
	82	6
4. *Breast*	94	2
5. *Lung*	20	0
6. *Miscellaneous*		
a. Skin	8	1
b. Melanoma	30	0
c. Soft tissue sarcomas	11	0
d. Synoviomas	3	0
e. Bone		
Osteogenic sarcoma	11	0
Ewing's sarcoma	8	0
f. Lymphomas	12	0
g. Unknown primary	38	0
	121	1

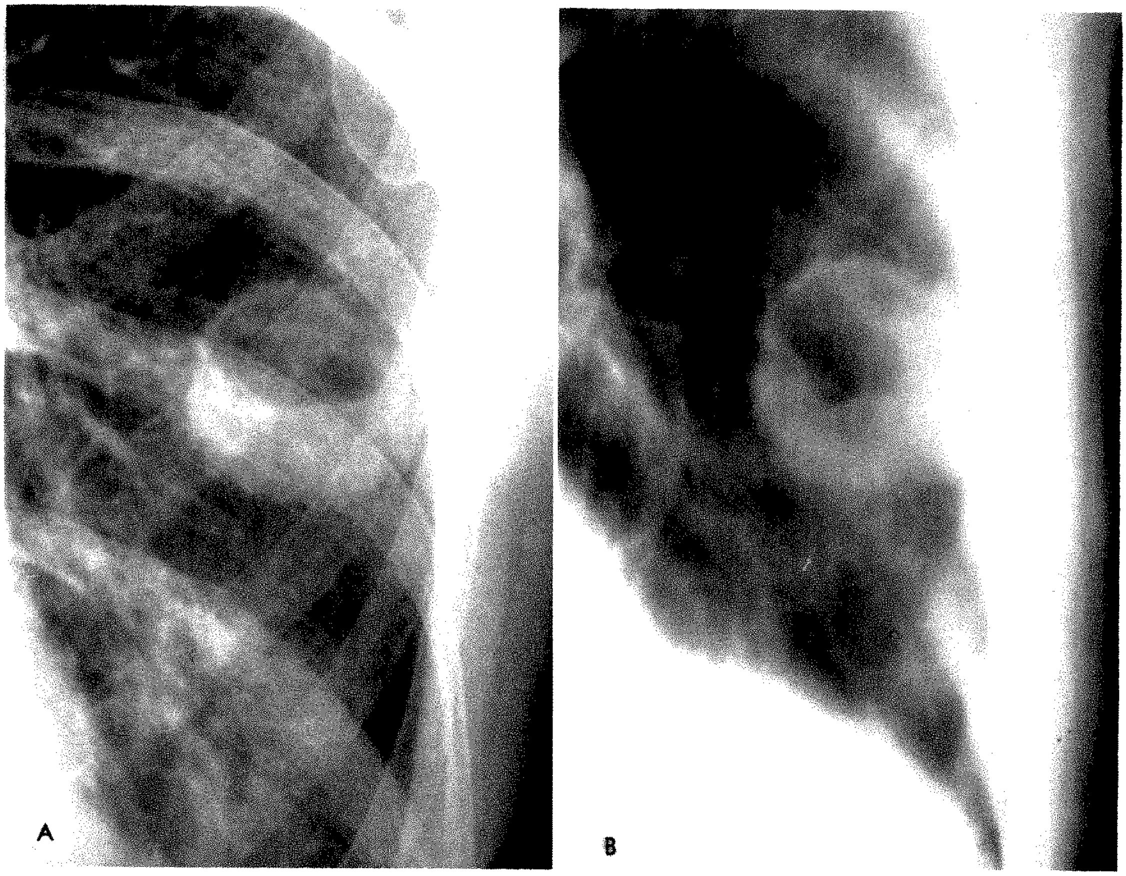

Fig. 1. Solitary excavating squamous cell carcinoma of lingula in a sixty-nine year old white female with previously treated squamous cell tumor of cervix. Histology was inconclusive as to whether this was a pulmonary primary tumor or metastasis. (*A*) Conventional erect posteroanterior roentgenogram of chest. Air-fluid level is present. (*B*) Laminagram in recumbent anteroposterior projection demonstrating the criteria of Wigh and Gilmore[37] for the diagnosis of excavating pulmonary neoplasms.

ever, so-called "ring shadows" were soon encountered, the walls of which were proved to be of neoplastic origin but so thin that, at times, all of the foregoing criteria did not apply (Fig. 2, *A* and *B*; 3, *A* and *B*; 4, *A* and *B*; 6, *A* and *B*; 7, *A* and *B*; and 8, *A* and *B*). In such instances, a stringent analysis of the composite shadows of the area was carried out. If any part of the ring wall could be considered vascular, pleural or of other extraneous origin, the diagnosis of cavitation was considered equivocal and the case discarded for purposes of this study.

In each instance the histopathology of the primary tumor has been carefully restudied. Where possible, proof of the neoplastic nature of the cavity has been obtained by autopsy or pulmonary resection and the histopathology of the metastatic lesion related to the primary tumor. In cases where this has not been feasible, reliance has been placed on roentgenographic criteria, serial examinations, clinical evidence of metastatic deposits elsewhere, and the absence of clinical or laboratory evidence of pulmonary inflammatory disease.

The incidence of cavitating bronchogenic carcinoma was also determined for comparative purposes.

INCIDENCE

Roentgenographically detectable cavitation was found in 9 per cent of primary lung tumors and 4 per cent of pulmonary metas-

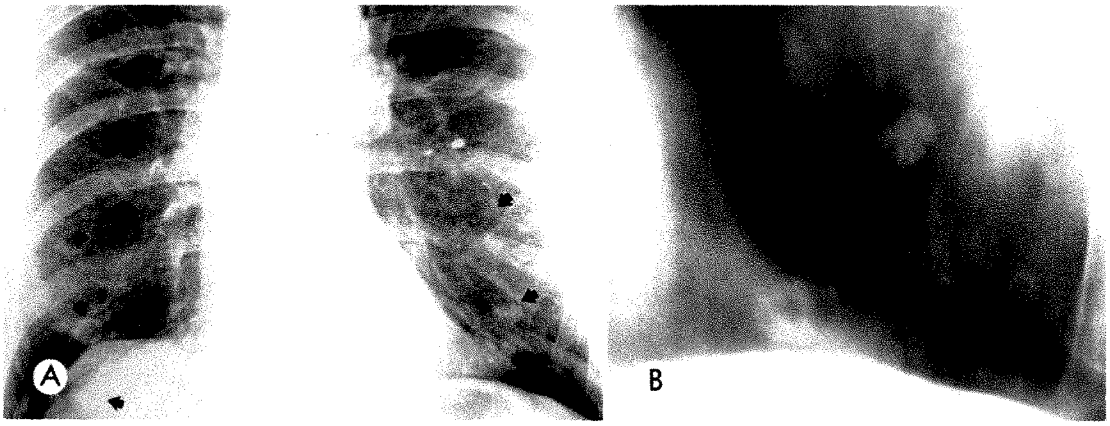

FIG. 2. Multiple excavating pulmonary metastases in a seventy-eight year old white male with Grade III squamous cell carcinoma of the ear. The tumor has widely infiltrated the parotid gland and the regional cervical lymph nodes. A marked tendency to central necrosis was evident in all biopsy specimens. (*A*) "Ring shadows" as well as apparently solid nodules are scattered throughout the chest. The largest nodule (right lower lobe) measures 1.5 cm. in diameter and shows extensive excavation. (*B*) Laminagram of left base showing neoplastic characteristics of a cavity in a 1.2 cm. nodule just above the diaphragm. The second metastatic deposit appears solid, but later showed excavation.

tases in this study. An additional 7 excavating neoplasms could not be placed in either category since all were solitary lesions of squamous cell origin, arising in patients with primary squamous cell carcinoma elsewhere. In all probability, the incidence of central excavation in metastases is higher than the figures indicate. An additional 20 cases were discarded in the absence of unequivocal roentgenographic proof of cavitation and no cases were included in which excavation was detected following chemotherapy or local roentgen therapy to the metastases. The results of the analysis are recorded in Table III.

HISTOLOGIC TYPES

Eleven, or 69 per cent, of the multiple excavating metastatic nodules were of squamous cell origin. All of the excavating bronchogenic carcinomas were of this cell type, a finding in agreement with other published series. The remainder of the metastatic group (5) were adenocarcinomas. Three originated in the colon and 2 in the female breast. The tendency of the pulmonary metastases of adenocarcinoma of the colon to excavate is emphasized when it is noted that the 3 cases in this series occurred in but 16 patients as contrasted to 2 examples in 94 patients with carcinoma of the breast. Le May[15] has also observed 4 cases occurring with carcinoma of the colon and Curran and MacCarthy[3] have recently reported a case.

Since the number of excavating metastases in the series is relatively small, we have attempted to confirm this distribution by investigation of material accumulated since February 1, 1957. The additional cases do not represent an exhaustive review of all metastatic disease as in the initial group, but are those routinely indexed in the course of daily film interpretation. Twelve examples of unequivocal excavating metastases were encountered; 9 of squamous or transitional cell type, 2 adenocarcinomas (breast and corpus uteri) and 1 melanoma. As in the previous group, almost an equal number were discarded since the roentgen findings were equivocal and 2 solitary lesions were listed which could not be differentiated from primary bronchogenic carcinoma. The locations of the primary tumors paralleled those of the first group studied. Analysis of the over-all distribution of tumors in this institution did not indicate a sufficient variation from those of the average community to invalidate these findings.[21]

Table III

RESULTS OF ANALYSIS OF 6,729 CONSECUTIVE CASES

A. Cases Reviewed (consecutive)		6,729
a. Malignant tumors of the lung		574 or 8.5% of total cases
1. Primary tumors of lung		176 or 2.6% of total cases
2. Metastatic tumors of lung		398 or 5.9% of total cases
B. Cases of Excavating Tumors		37
a. Bronchogenic carcinoma		16 or 9.1% of primary tumors
b. Metastatic tumors		16 or 4% of metastatic tumors
c. Primary vs. solitary metastatic tumors		7 or 17.9% of excavating tumors
C. Multiple Excavating Metastases		
Site of Primary	No. of Cases	Cell Type
a. Pharyngo-larynx	4	Squamous
b. Female genitalia	5	Squamous
c. Skin	1	Squamous
d. Urinary bladder	1	Transitional
e. Colon	3	Adenocarcinoma
f. Breast	2	Adenocarcinoma
D. Excavating Primary vs. Solitary Metastatic Tumors		
Site of Primary	No. of Cases	Cell Type
a. Uterine cervix	3	Squamous
b. Pharyngo-larynx	2	Squamous
c. Skin	1	Squamous
d. External genitalia	1	Squamous

PATHOGENESIS

The reasons for the assumption that necrosis in pulmonary tumors is attributable to an inadequate blood supply have been summarized by Willis[38] as follows: (1) the vascular supply of most pulmonary tumors of epithelial origin is richest at the margins; (2) short of actual necrosis, many features indicative of inadequate cellular nutrition or oxygenation are frequently noted microscopically; and (3) degenerative changes are common both at autopsy and microscopically in pulmonary tumors which exceed several centimeters in diameter. Presumably, as the growing tumor outstrips its blood supply, central ischemia occurs with ensuing necrosis. Infection may or may not supervene. Roentgenographically, necrosis becomes evident when communication with a regional bronchus permits expulsion of the necrotic material.

As the review of our series progressed, some doubt was cast upon the complete validity of this explanation by three factors: (1) the extremely small size of many of the necrosing tumors; (2) the thinness (1–2 mm.) and internal smoothness of the walls of many cavities; and (3) the predominance of squamous cell lesions. Discussion of the problem with pathologists also indicated that the majority of central degenerative changes seen at autopsy were of a gelatinous or caseous nature rather than actual cavitation. For these reasons other explanations were sought.

The possibility of implantation of tumor cells by aspiration was considered since many of the primary lesions were located in the head and neck area. It was also postulated that metastases of this type would tend to be less vascular and hence more likely to necrose at an early stage. However, this explanation was largely discarded when it became evident that direct exfoliation of cells into airway was not probable in the majority of our cases and that primary lesions elsewhere in the body resulted in identical forms of cavitating metastatic disease in the lungs. Aspiration spread cannot be entirely dismissed on these grounds,

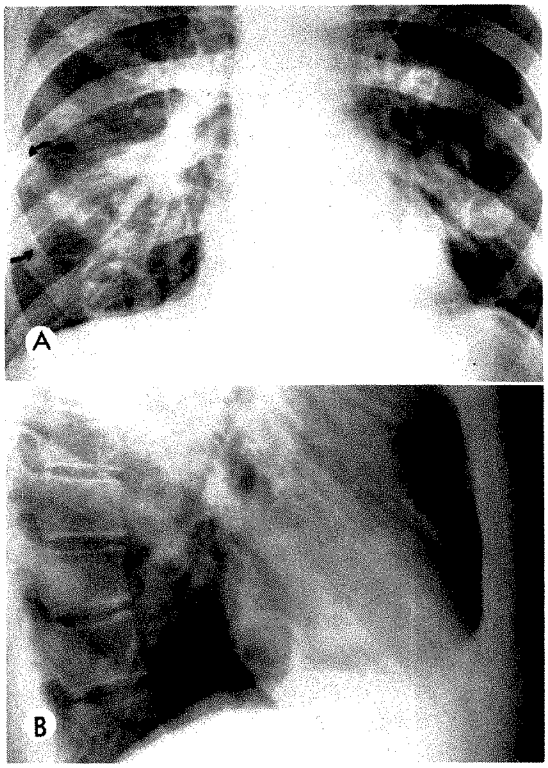

Fig. 3. (*A* and *B*) Multiple excavating pulmonary metastases in a forty-four year old white male with Grade II squamous cell carcinoma of the skin invading the parotid gland and the regional lymph nodes. Microscopically, the tumor showed intracellular keratin and pearl formation; the lymph node metastases were anaplastic with central degeneration. Fluid levels are present in the larger metastases. The arrows in *A* indicate smaller excavating deposits. Note relative uniformity of all wall thicknesses despite the size of the metastases.

but Liebow[17] has described such tumors as largely intrabronchial and polypoid with a relatively small base of attachment. This description did not apply in any of the cases in our series in which resection or autopsy was done and proved cases in the literature are comparatively rare. Willis[38] has pointed out that three factors usually prevent engrafted disease in the respiratory tract: (1) the mucoid character of the bronchial secretions tends to prevent implantation of cells, (2) the normal bacterial flora of the respiratory tract destroys malignant cells, and (3) respiratory motion and ciliary activity of the respiratory epithelium prevent effective implantation of foreign particles.

Mayock *et al.*[20] have demonstrated that cavitation can be simulated by lesions filled with solid or liquid caseous material and suggest that this results from a physiochemical change which increases the lipoid concentration of the contents. Curran and MacCarthy[3] cite this as a possible explanation for the apparent cavitation of pulmonary metastases from an adenocarcinoma of the rectum. In their case, expectoration was not a prominent feature and no communication of the multiple cavities with the bronchi could be shown. However, the presence of air-fluid levels in several of the cavities illustrated affords at least *prima facie* evidence of communication with the airway. Although this hypothesis might explain the apparent excavation of some of the lesions in our series, the frequent presence of air-fluid levels has been accepted by us as a reliable indication of continuity with the respiratory passageways.

Simon[33] has noted in his recent text that small and thin-walled cavities ("ring-shadows") may be neoplastic in nature. Since there is often no history of copious expectoration, he regards it as unlikely that the central air space has resulted from expulsion of the necrotic material. He suggests that in its early stages a growth may obstruct a relatively small bronchus and cause cystic distention of the air sacs distal to the block; subsequently, the neoplasm grows into the cyst forming a secondary lining of tumor cells.

Anderson and Pierce[1] postulate a similar mechanism for the occasional primary squamous cell carcinoma of the bronchus which resembles a thin-walled cyst. Examination of their operative and necropsy specimens in 6 cases revealed the linings of the cavities to be smooth and shining in some areas and rough and opaque in others. The cavity walls were composed of a mixture of fibrous tissue and well-differentiated squamous carcinoma cells. The inner surface of the cavities consisted either of these cells or of flattened squamous metaplastic

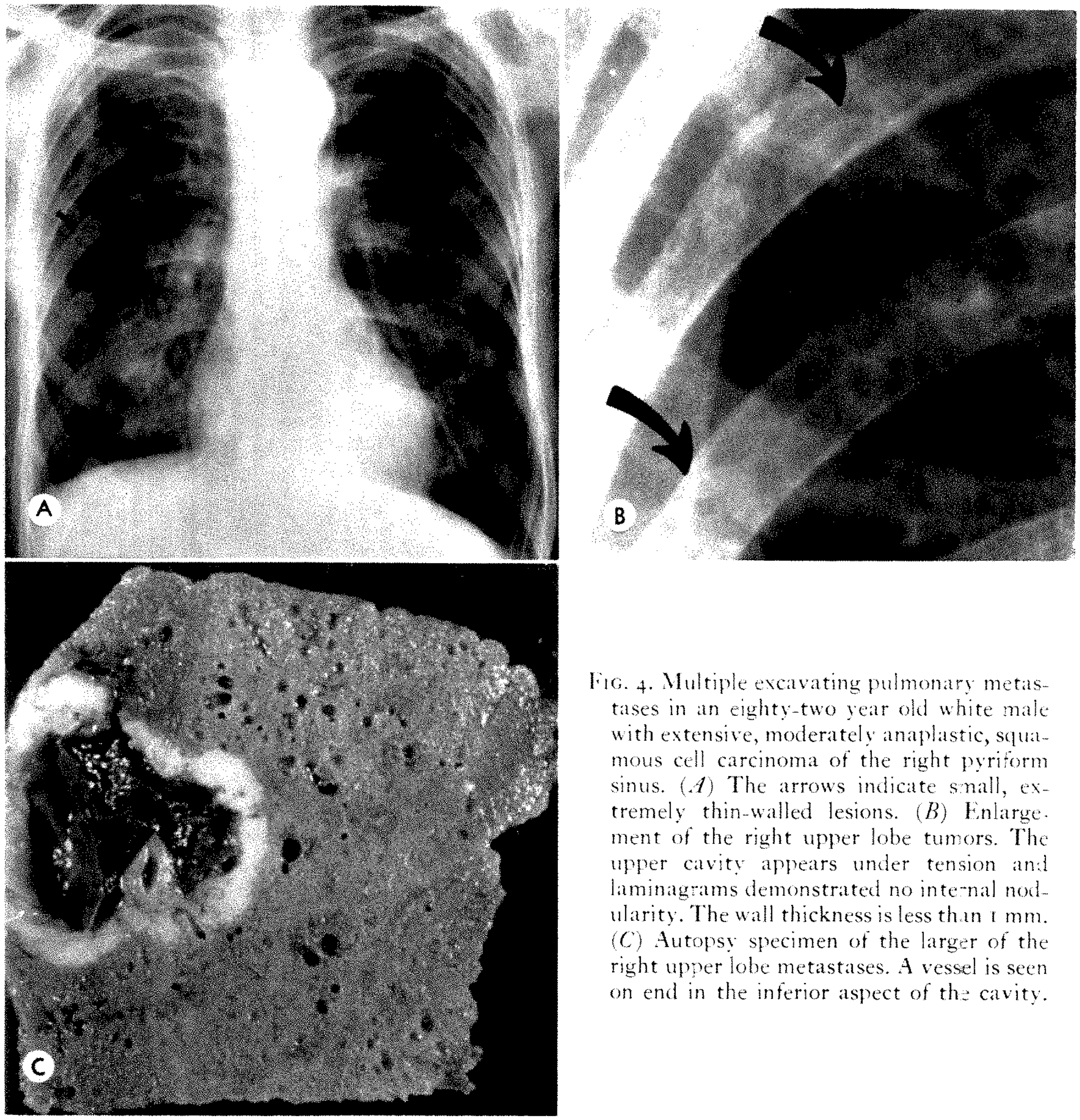

Fig. 4. Multiple excavating pulmonary metastases in an eighty-two year old white male with extensive, moderately anaplastic, squamous cell carcinoma of the right pyriform sinus. (*A*) The arrows indicate small, extremely thin-walled lesions. (*B*) Enlargement of the right upper lobe tumors. The upper cavity appears under tension and laminagrams demonstrated no internal nodularity. The wall thickness is less than 1 mm. (*C*) Autopsy specimen of the larger of the right upper lobe metastases. A vessel is seen on end in the inferior aspect of the cavity.

epithelium with malignant tissue spreading just beneath the surface. The layers of malignant cells were frequently thin and portions of the walls were formed by compressed lung only. Occasionally, a thin covering of inflammatory material was present. In no instance was degeneration or necrosis of the malignant cells noted. In view of the marked variance between these findings and the gross and histologic appearance of the usual excavating pulmonary tumor, these authors suggest that this form occurs when a thin layer of malignant cells grows into a pre-existing cavity. Such cavities may be formed by a ball-valve obstruction of a bronchus or by inflammatory changes in proximity to, but not involving, the tumor. Although unable to demonstrate positive evidence of a ball-valve obstruction in their cases, they regard the presence of a lining membrane of nonmalignant epithelium as conclusive proof of their hypothesis.

The gross and histologic findings in many of the excavating squamous cell metastases in this series were similar to those de-

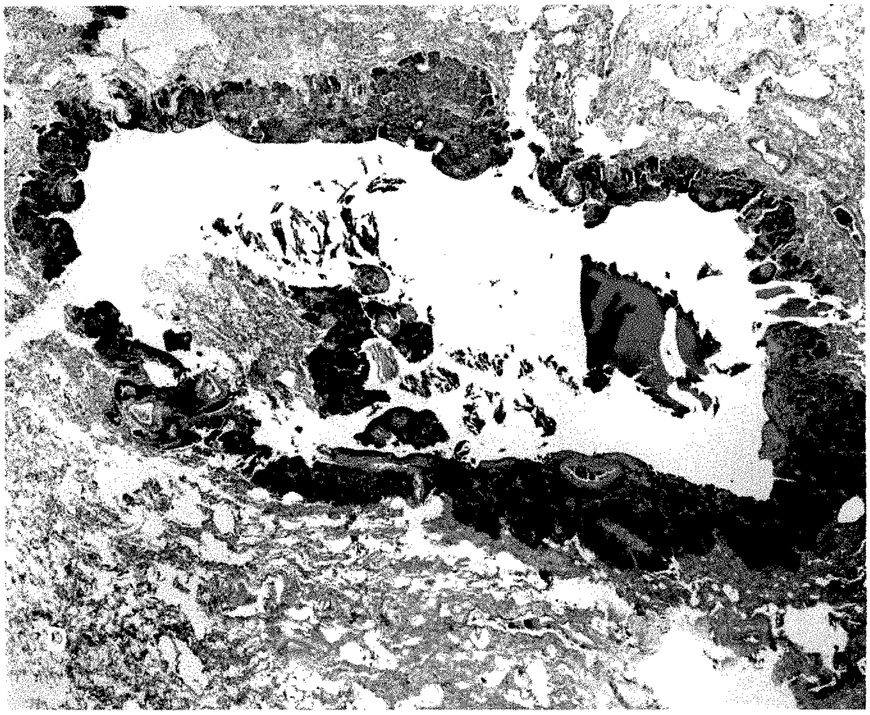

FIG. 4. (*D*) Tissue section through Figure 4*C*. The contents are artifacts. The walls are composed of malignant squamous epithelium with little evidence of degeneration. Although no definite connection with airway was demonstrable on serial sections of entire cavity, it is believed that cornified central layers have desquamated or been stripped away by respiratory motion and evacuated.

scribed by Anderson and Pierce (Fig. 4, *C* and *D*; 5, *A* and *B*; and 6 *C*). As noted by Seaman and Arneson,[30] it is often impossible to differentiate between squamous cell metastatic deposits and primary squamous cell bronchogenic carcinoma on histologic grounds alone (Fig. 1, *A* and *B*). It is also of interest that cystic metastatic deposits derived from adenocarcinoma of the colon are roentgenographically indistinguishable from the squamous cell variety (Fig. 8, *A* and *B*). Nevertheless, it does not seem reasonable to us to assume that multiple metastatic deposits would, either fortuitously or selectively, invade multiple pre-existing cavities.

The frequency of cases of excavating squamous cell tumors reported in the literature and in this series suggests that inherent properties of the normal primary tissue are a potentiating factor in the development of cavitation. In any stratified epithelial membrane which is exposed to air, the surface cells dehydrate and fuse to form a protective layer of keratin. As the deeper cells reproduce, new cells are constantly pushed toward the surface where they in turn are converted into keratin to replace desquamated layers. The same process often occurs in the center of squamous neoplastic masses but, in the absence of air, the end-product is semiliquid as contrasted to the horny character of surface keratin (Fig. 5*A*). In general, since metastases of most tumors closely reflect the structural features of the primary lesion, the degree of cornification in the metastases will parallel that of the primary tumor. This process is most evident in squamous tumors of the head and neck and, to a lesser extent, in those of the cervix and bladder. Various authors[12,30,35] have commented upon the cystic tendencies of squamous cell metastases in the lymph nodes and abdominal viscera, particularly from these locations. It is therefore not surprising that similar

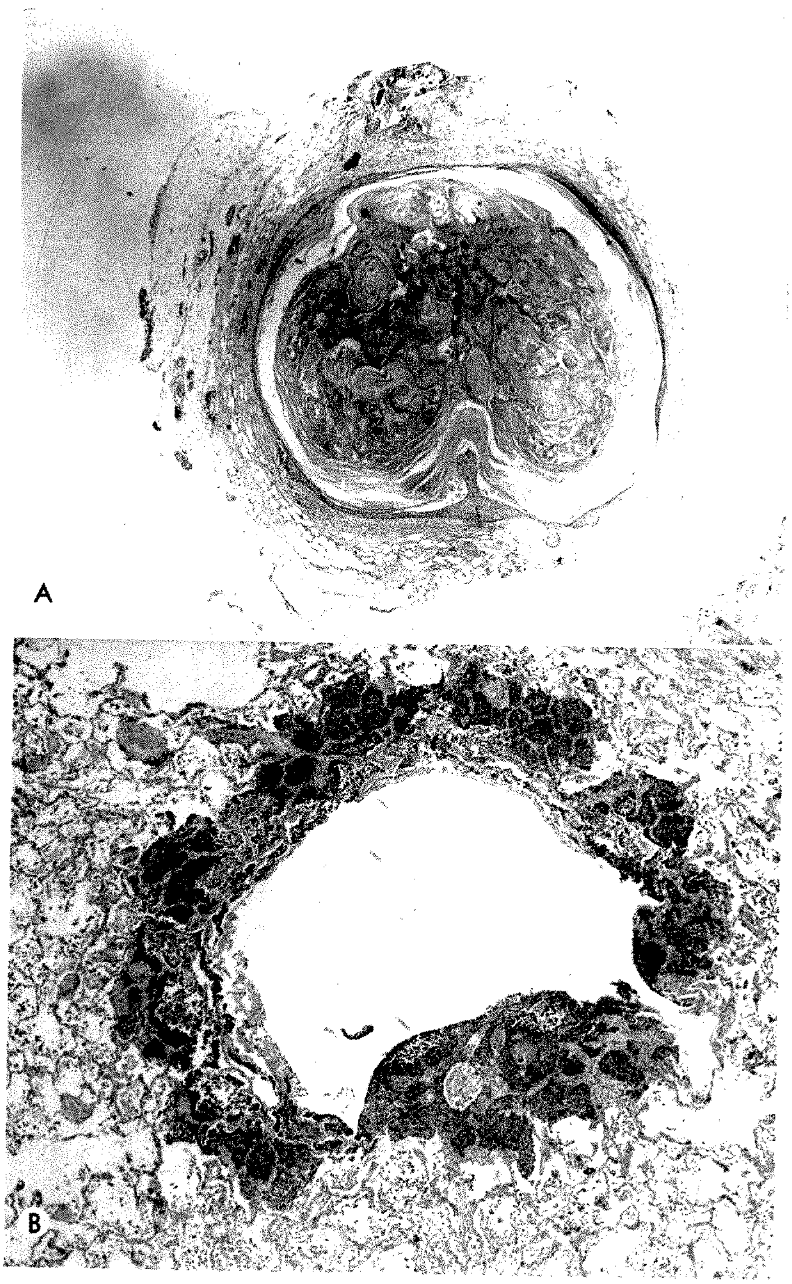

FIG. 5. Central cornification of malignant squamous epithelial masses. (*A*) Tumor-invaded lymph node from a patient with squamous cell carcinoma of the lip. Little normal architecture remains. An extremely thin layer of viable malignant squamous epithelium lines the capsule of the node; the contents largely consist of multiple layers of cornified epithelium, epithelial pearls and cellular debris. Such nodes are cyst-like on palpation, the cornified material being semiliquid in the absence of air. (*B*) A 2 mm. metastatic pulmonary nodule from the same patient illustrated in Figure 4. This was not detected roentgenographically. Note the extensive central excavation with lack of debris and little evidence of degeneration of neoplastic cells. There is probably a connection with an alveolar duct; a thin layer of tumor cells lines the duct walls. It is thought that such communications with the lesser respiratory passages permit early evacuation of the semiliquid products of cornification, leaving only the thin rim of viable tumor cells.

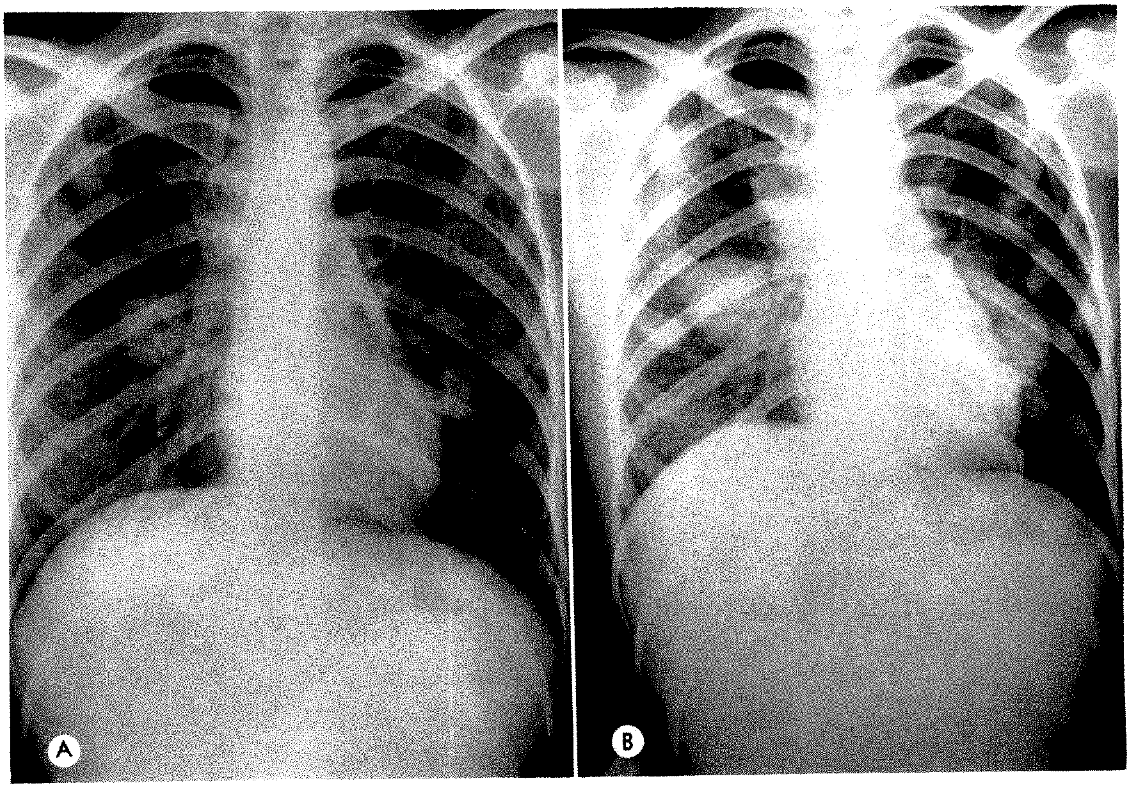

FIG. 6. Multiple excavating pulmonary metastases in a twenty-six year old white female with disseminated medullary carcinoma of breast. (*A* and *B*) Cavitation of the type described by Wigh and Gilmore.[37] In the forty-four day interval between roentgenograms, the metastases have increased in size, but the cavities have disappeared or are partially filled, presumably as the result of bronchial obstruction.

metastatic forms occur in the lungs. As a rule, in our group of cases, metastases from the head, neck and skin showed earlier and more extensive excavation than those from the cervix and bladder.

The fact that a squamous metastatic deposit may have a semiliquid center does not in itself explain the relative frequency of roentgenologically demonstrable cavitation. In the usual course of events,[38] following occlusion of an arteriole by a viable thrombus of tumor cells, the vessel wall is invaded and access to the perivascular spaces is gained. The tumor may then spread interstitially or intra-alveolarly. The latter is a frequent method of extension, the tumor employing the alveolar spongework as a stroma and extending progressively via the antra or Kohn's pores. The neoplastic tissue is avascular, the blood supply being derived from the alveolar septa. Eventually the lung architecture is destroyed in the substance of large tumors and central avascular necrosis ensues (Fig. 6 *C*). Ellis *et al.*[6] have shown that, although metastatic disease commonly involves the bronchi, the overlying bronchial mucosa usually remains intact. These authors cite this finding as an explanation for the low incidence of positive cytologic studies in metastatic disease. Since the majority of metastatic tumors undergo central degeneration only when the tumor exceeds the available blood supply, the low incidence of roentgenologically demonstrable cavitation may be similarly explained.

It is our belief that a clue to the preponderance of squamous cell lesions may be found in the extremely small metastatic deposits which have undergone extensive central excavation (Fig. 2–5, inclusive). The size of these metastases makes it highly

FIG. 6 (*C*) Tissue section of pulmonary metastasis. Note the central debris and gradual transition from viable tumor to necrotic material in contrast to the sections through the thin-walled cavities of squamous origin.

improbable that inadequate circulation is responsible for the central degeneration. However, central cornification, as an inherent characteristic of squamous epithelium, may begin almost immediately. As the tumor breaks into the alveoli, multiple opportunities for communication between the semiliquid contents and the respiratory passageways below the bronchial level occur (Fig. 5, *A* and *B*); the alveoli and alveolar ducts may be considered analogous to the "pre-formed cavities" suggested by Anderson and Pierce[1] and by Simon[33]. Once the central layers of epithelium are in contact with air, the process of cornification is further facilitated and respiratory motion assists in stripping the dehydrated, stratified material from the cavity walls. Growth meanwhile progresses peripherally, the two processes combining to increase the size of the cavity while maintaining a wall of relatively constant thickness (Fig. 7, *A* and *B*).

Adenocarcinomas may show a cystic tendency throughout the life of a tumor, presumably due to the transmission of secretory function to the metastatic deposits. Large quantities of mucin and pseudomucin may be produced, particularly by tumors primary in the gastrointestinal tract, ovary and breast. However, true mucin-secreting carcinomas occur in but 10–15 per cent of cases, mucoid degeneration of primary and secondary adenocarcinomas being more commonplace. The relationship, if any, of these processes to the excavating forms of pulmonary metastases is not clear. Both cystic and thick-walled cavities occur, the former most notably with carcinomas of the colon. Only one mucin-producing carcinoma was encountered in this series and the case illustrated in Figure 8, *A* and *B* was a well-formed adenocarcinoma in which mucin production or degeneration was not a prominent feature. Willis' contention that the pulmonary metastases of well-differentiated adenocarcinomas—particularly the mucoid variety—tend to spread via the septal pores and palisade directly upon the

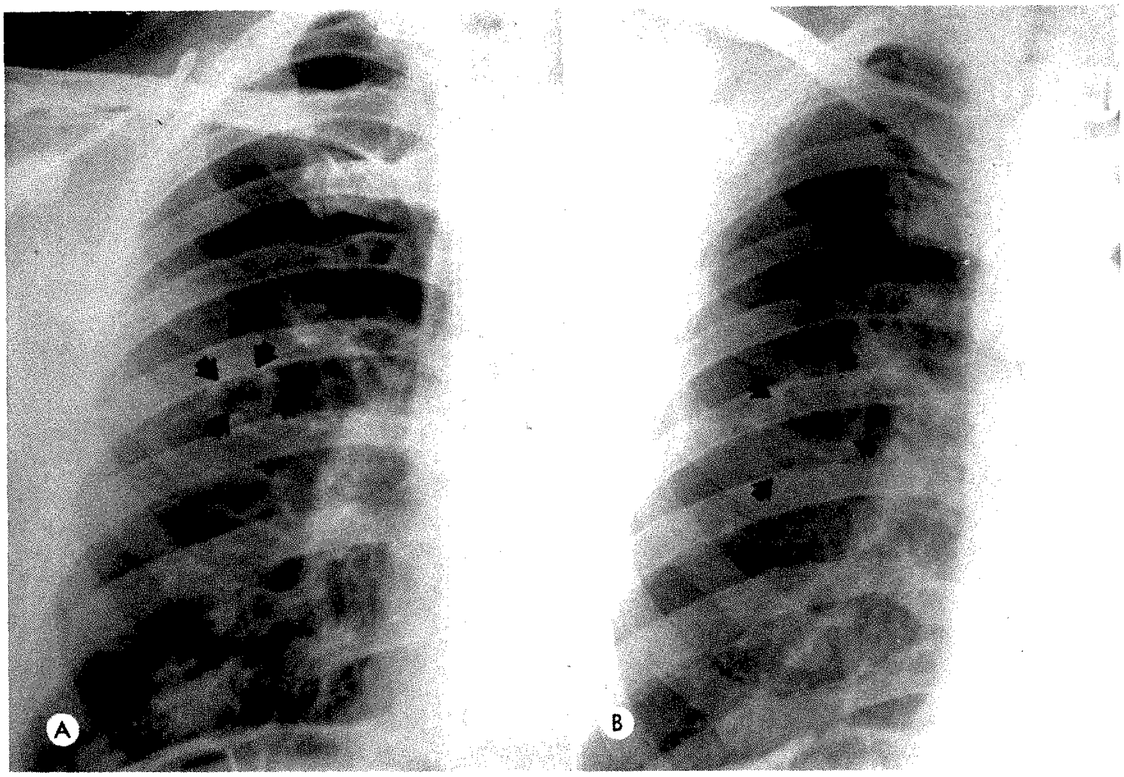

Fig. 7. (*A* and *B*) A sixty-nine year old white male with Grade III squamous cell carcinoma of the buccal mucosa. Microscopically, keratinization and pearl formation were prominent. In a two month interval between *A* and *B* the excavating metastases have increased in size, but the wall thickness remains approximately the same (2–3 mm.).

alveolar walls may be of significance.[38] But this description is disputed by some pathologists who feel that palisading is indicative of alveolar cell carcinoma, a form of tumor in which cavitation is seldom seen. Unfortunately, the tissue specimens available to us are insufficient to establish a relationship between any of these factors and excavation. Nevertheless, it seems evident that the existence of the cystic forms implies the presence of a factor or factors other than a locally inadequate blood supply.

In any form of thin-walled pulmonary cavity, an alternately smooth and crenated appearance of the external wall suggests the presence of an intermittent ball-valve bronchial obstruction (Fig. 4, *A* and *B*; 7, *A* and *B*; and 8, *A* and *B*). It is probable that such a mechanism assists in the growth of cystic neoplastic cavities. Rupture of the thin layer of tumor cells and adjacent devitalized alveoli by increases in intracavitary pressure may explain the interspaced areas of nonmalignant living tissue noted by Anderson and Pierce[1] as well as contribute to the size of the cavity.

Failure of uniform behavior by all metastases of a given tumor or group of tumors is attributable to variations in the individual neoplasms as well as to departures from parenteral structural type by the metastases. For example, not all excavating pulmonary metastases in this series from the head and neck were of the "ring" or cystic type. The same is true of the adenocarcinoma group. Presumably, those metastases which show the more typical appearance of excavating pulmonary neoplasms depend upon chance destruction of the bronchial cartilage and mucosa for expulsion of their contents; *i.e.*, the factors

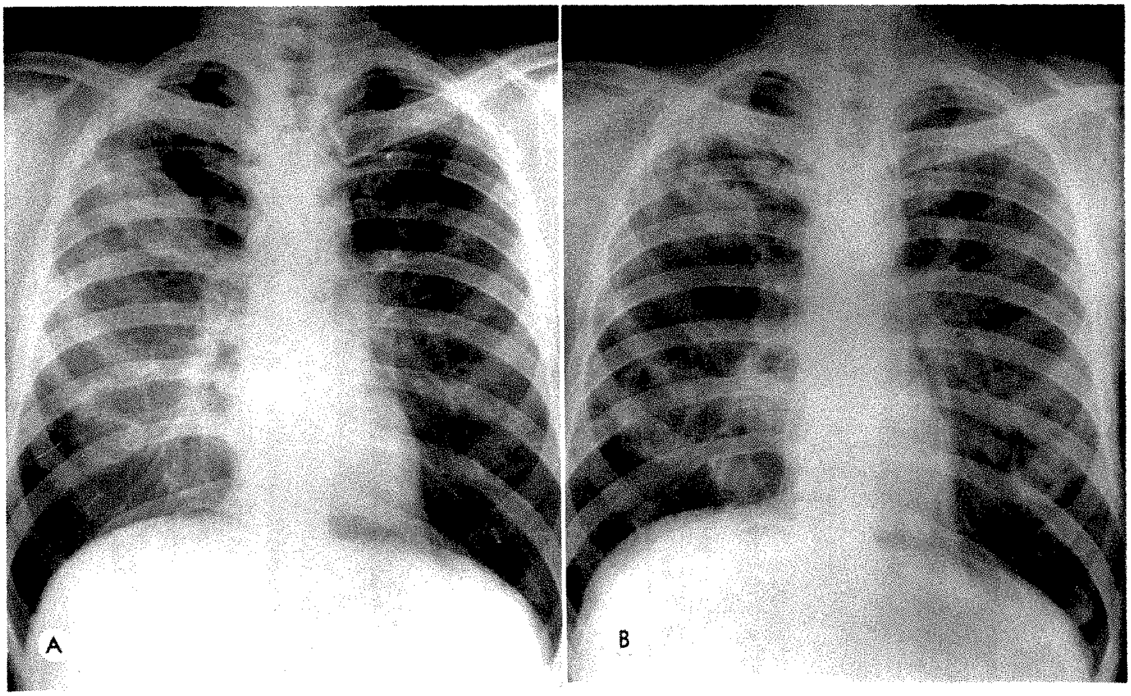

Fig. 8. Multiple excavating pulmonary metastases in a forty-six year old white male. Thirty months previously an abdominal-perineal resection had been performed for a well differentiated, nonmucoid adenocarcinoma of the rectum. The pulmonary biopsy of the right upper lobe lesion revealed a well differentiated adenocarcinoma. (Courtesy of Dr. Marjorie Le May, Boston, Massachusetts.) (*A*) Diffuse inflammatory disease involving cystic metastases of the right upper lobe. Temperature 103° F. The pneumonic process was not present on a roentgenogram made four days previously. (*B*) Seven-month follow-up roentgenogram. The metastases have increased in size and number, but the cavity walls maintain average thickness. Inflammatory disease has partially obliterated right upper lobe cavities. The large right lower lobe cavity is more irregular, suggesting the presence of intermittent ball-valve mechanism.

permissive of communication with the airway below the bronchial level are not sufficiently pronounced to allow formation of a cystic cavity. However, the relative frequency of thick-walled squamous and adenocarcinomatous metastatic cavities as compared to other cell types would indicate that these characteristics, though less effective, facilitate excavation (Fig. 9, *A* and *B*).

Cavitation in other forms of metastatic tumor is, in the majority, the result of inadequate blood supply. It should be borne in mind, however, that reported instances of necrosis in teratomas may well result from breakdown of epithelial elements. Necrosing "seminomas" may be included in this category since a biopsy of one site may be indicative of seminoma, but in other areas may contain teratomatous elements (Willis[38]).

Pancreatic neoplasms may produce metastases which retain the capacity to secrete the proteolytic and lipolytic enzymes. The functioning metastases in effect digest both their own substance and the surrounding normal tissue. None of these have been encountered in this series, but such instances are recorded in the literature.

ROENTGENOGRAPHIC CONSIDERATIONS

Cavitating metastases may be single or multiple and vary greatly in size. Relatively massive lesions may be present without apparent excavation, whereas smaller deposits may, in the same patient, show central degeneration. The smallest metastatic cavity detected in this series was 8 mm.

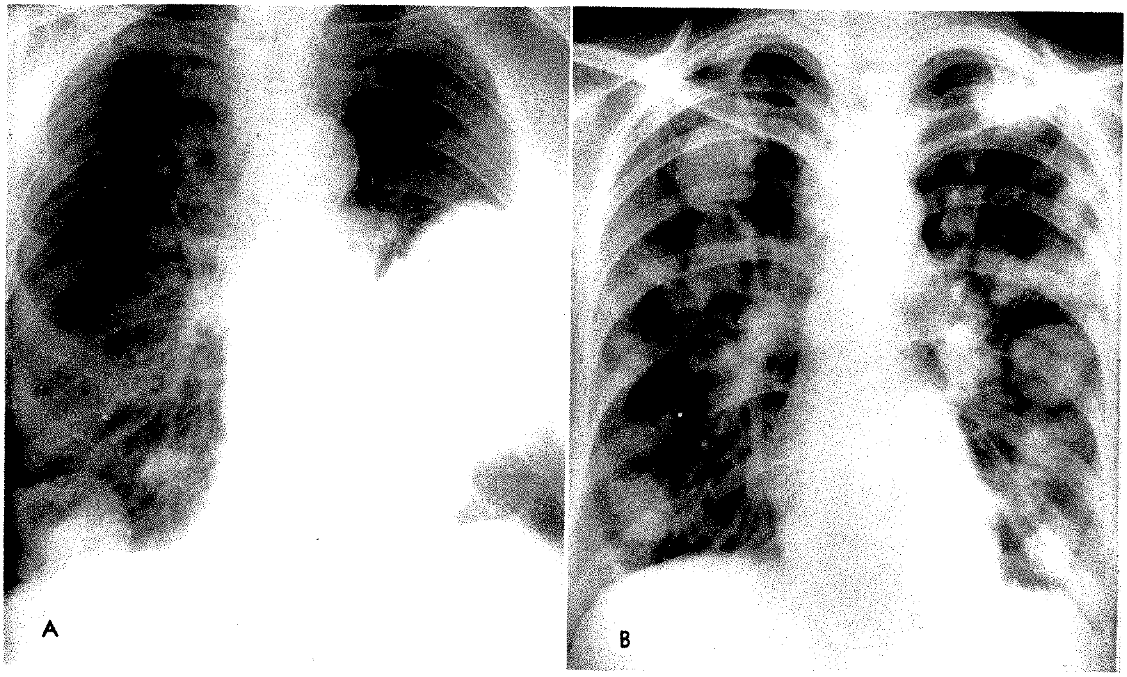

FIG. 9. Noncystic excavating pulmonary squamous cell carcinoma metastases. (A) Seventy-one year old white male. Primary lesion, Grade II papillary transitional cell carcinoma of the urinary bladder. Excavation was demonstrable only in the smaller mass. (*B*) Thirty year old white female. Primary lesion, Grade III squamous cell carcinoma of the cervix.

in diameter. If it is correct that tissue characteristics are responsible for cavitation, then it would seem logical to infer that similar changes are also present in at least some of the apparently intact nodules. The solid appearance may stem from lack of communication with a bronchus, intermittent bronchial obstruction or variations in the transmitted structural details of the metastases. Cases of unequivocal cavitation in a nodule have been observed in this series with the same lesion appearing as a solid mass on subsequent studies (Fig. 6, *A* and *B*). Evacuation of other nodules may occur during the same interval. Fluid levels are frequently seen, particularly in the larger metastases (Fig. 3, *A* and *B*; 8, *A* and *B*; and 9*A*).

The shape of thin-walled metastatic deposits may be quite bizarre, the appearance suggesting multilocular cystic disease rather than tumor. Occasionally, these will assume a more typically spherical contour, probably as the result of intermittent bronchial obstruction. Despite progressive increase in the size of the cavity, the walls are prone to maintain an average thickness, a finding which supports the theory that the older cells are shed internally.* In some instances intermittent bronchial obstruction may also be a factor in maintaining the average wall thickness (Fig. 7, *A* and *B*; and 8, *A* and *B*).

Although as a rule the criteria of Wigh and Gilmore[37] serve as reliable diagnostic signs, the nodularity of the inner wall may not always be apparent on plain roentgenograms of thin-walled lesions. Usually, this can be demonstrated by laminagraphy (Fig. 2*B*). Less commonly, the inner wall is smooth and the correct diagnosis becomes dependent upon the demonstration of solid

* The absence of significant quantities of sputum clinically does not rule out communication with the airway. The process begins early and progresses slowly with the size of the cavity dependent upon respiratory dynamics as well as tumor growth. Unless substantial bronchial obstruction occurs, only minute quantities of debris are expelled.

or cystic deposits elsewhere (Fig. 4, *A* and *B*).

Although relatively nonspecific, the identification of excavating pulmonary metastases does permit some generalization concerning their origin. Approximately 70 per cent of these will be of squamous cell origin. In the male, the bulk arise from tumors of the head and neck; in the female from the genitalia. The number of adenocarcinomas has been small, but there is no significant sex preference in the cases seen and the pulmonary forms are indistinguishable from the squamous variety. In general, the metastases originating in the head and neck undergo cavitation when quite small and have extremely thin walls. The excavating lesions of the bladder and genitalia on the whole have thicker walls and resemble the more common form of excavating pulmonary neoplasm (Fig. 9, *A* and *B*).

Spontaneous pneumothorax occurring with metastatic pulmonary cancer has been reported by several authors.[14,18,32] With the exception of one case of metastatic adenocarcinoma reported by Sherman and Brant,[32] all of these have been metastasizing sarcoma. In several instances there has been cavitation of the metastatic deposits, but the majority show spontaneous pneumothorax without obvious cavity formation. None of our cases demonstrated pneumothorax despite some instances of extensive cavitation, and pleural effusions were not common.

DIFFERENTIAL DIAGNOSIS

There are several entities which may be confused with excavating metastatic deposits in the lungs. The difficulty of differentiating between a bronchogenic carcinoma and a solitary necrosing metastatic deposit has already been discussed. Felson[8] has referred to a case of an apical cavity which was initially 8 mm. in diameter with a wall 2 mm. in thickness. This was observed over a period of approximately two years and in no instance did the wall thickness exceed 3–4 mm. even though the diameter of the cavity steadily increased. In the absence of disease elsewhere, this was felt to represent a primary bronchogenic carcinoma. At least 4 cases of bronchogenic carcinoma with excavating pulmonary metastases have been encountered in this institution subsequent to analysis of this series.

Smaller pulmonary cysts may be confused with thin-walled cavitating nodules, especially when repeated bouts of inflammatory disease in the cysts have distorted the margins. Peabody *et al.*[24,25] have reported an example of bronchial carcinoma arising in a lung cyst.

Multiple pulmonary abscesses, particularly those which occur with staphylococcic pyemias or showers of small septic emboli may produce well defined densities highly suggestive of nodular metastases. With the development of central destruction, cavitation with fluid levels may be evident.[28]

In the granulomatous group of lesions, the cavities found in aspergillosis, coccidiomycosis and chronic tuberculosis represent the more important differential entities.

Less commonly, varicella pneumonia may appear as well circumscribed nodular deposits in the lung fields which subsequently excavate, the roentgen appearance being indistinguishable from that of excavating metastases.[16] Forsee and Blake[9] have reported 4 patients with systemic xanthomatoses in which sharply defined pulmonary nodules and concomitant cyst-like changes in the lung were demonstrable. These resulted from obstruction of bronchi by submucosal infiltration of xanthoma cells.

SUMMARY AND CONCLUSIONS

1. Sixteen new cases of excavating pulmonary metastases are presented.

2. In a series of 6,729 consecutive patients seen in a tumor institution, excavation was encountered in 9 per cent of patients with primary tumors of the lung and 4 per cent of patients with pulmonary metastases.

3. Sixty-nine per cent of the excavating metastases were of squamous cell origin as

were all of the bronchogenic carcinomas. Thirty-one per cent were derived from adenocarcinomas of breast and colon. This distribution was paralleled in a control series of patients (12 cases).

4. The possible mechanisms of excavation are discussed. It has been concluded that specific tissue characteristics are primarily responsible for the majority of roentgenographically detectable excavating metastases rather than deficiency in the blood supply *per se*.

5. The roentgen criteria and differential diagnosis of excavating pulmonary neoplasms are enumerated and the feasibility of identifying the primary tumor from the characteristics of its metastases is considered.

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PRIMARY LYMPHOSARCOMA OF THE LUNG*

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LYMPHOSARCOMA may occasionally arise primarily in the pulmonary parenchyma without involvement of lymph nodes or other organs until late in the course of the disease. This localized form of the disease is an entity clinically separate from generalized lymphosarcoma. It is not certain if it is a malignant process from its inception or if it represents malignant degeneration of a so-called "benign lymphoma." The tumor is relatively slow growing and remains limited to the lung for variable periods of time. Because of this, treatment in the form of excision or irradiation should be designed to be curative rather than palliative as the prognosis, in those cases which have not metastasized, is good.

Since it involves only the lung, lymph node biopsy, marrow studies and other procedures used in the study of generalized lymphosarcoma are of no value in the diagnosis of primary pulmonary lymphosarcoma. The problem resolves itself into one of a mass in the lung of unknown etiology. Although the ultimate diagnosis in most cases will have to be made at the time of thoracotomy, certain clinical and roentgenographic features can suggest the diagnosis preoperatively.

Primary lymphosarcoma in the lung is quite rare. Robbins,[23] in a review of 715 cases of all types of lymphoma of which 7 per cent showed roentgen evidence of pulmonary involvement, found none which could be considered primary in the lung. Only 1 of the 196 cases of lymphosarcoma reported by Sugarbaker and Craver[32] was felt to arise in the lung and none of the 220 cases of lymphosarcoma in the series of Gall and Mallory.[10] Thus, a primary localization of lymphosarcoma in the lung is less common than it is, for example, in the stomach, tonsils or nasopharynx.

We have found 34 documented cases of primary pulmonary lymphosarcoma in the literature. A review of these cases together with 5 to be reported constitute the material for this report. Our cases were drawn from the Surgical Pathology files of The University of Michigan Medical Center and have all been proved by study of the specimen removed or biopsied at the time of thoracotomy.

REPORT OF CASES

CASE I. J.J., No. 632–681, a thirty-seven year old white female, was well until February, 1946, when she developed right sided pneumonia and pleurisy. This responded to treatment but she continued to have pain in the right lower thorax on deep inspiration. A year and a half later, following an upper respiratory infection, she felt weak and tired and began to cough, producing small amounts of grayish, odorless sputum. Her local physician noted clubbing of the fingers at this time. Cough and pleuritic pain continued until her admission to University Hospital on March 7, 1948. There was a ten pound weight loss over the previous year.

Positive physical findings were limited to the chest and the clubbing of the fingers. Routine laboratory studies were within normal limits. A roentgenogram of the chest (Fig. 1) revealed a homogeneous consolidation of the right lower lung. A bronchogram (Fig. 2) showed incomplete filling of the right lower lobe branches. The distal bronchi were tapered and some appeared to be compressed and displaced by the mass. At the time of bronchoscopy, the mucosa of the right lower lobe bronchus was found to be edematous and hyperemic. The basilar divisions were patent, although there was some narrowing of the posterior and mesial basal segments.

On April 21, 1948, thoracotomy was per-

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formed. The right lower lobe was found to be adherent to the chest wall. When this lobe was palpated through the long fissure, small nodules could be felt throughout its substance. The lung was fixed to the diaphragm. Exploration of the hilus showed tumor extending into the mediastinum. The tumor was biopsied and the chest closed. The microscopic diagnosis was lymphoblastoma infiltrating the lung.

Irradiation of the right lung and mediastinum was accomplished through anterior, posterior and right chest fields, using 200 kv., half value layer 1.0 mm. copper, focus skin distance 50 cm. A dose of 1,225 r in air was delivered to each field in a total of nineteen days. The patient has done well since her irradiation although she notices occasional blood streaking of her sputum. She underwent a subtotal gastrectomy for ulcer in 1951 without incident and was last heard from on February 17, 1958 at which time she was in good health.

Case II. F.M., No. 703-049, a sixty-four year old white male, was first seen at University Hospital on April 18, 1951 because of a bursitis of the left shoulder. A minifilm of the chest at this time showed a lesion in the left upper lung that was interpreted as localized pleural thickening. The patient was seen again in September, 1952 at which time he was asymptomatic. A chest roentgenogram (Fig. 3) once more showed the left upper lobe abnormality which had not changed over the past eighteen months. Bronchograms at this time were completely negative, the left upper lobe bronchi being of normal caliber and pursuing a normal course. Because of these findings it was felt that this lesion was not neoplastic and it was elected to continue observation of the patient. No change was noted during his examination in October, 1953 and the patient was not seen again until 1956 when comparison of a mobile survey chest roentgenogram made at that time with our previous roentgenograms showed some increase in the size of his pulmonary lesion.

He was admitted to University Hospital on September 27, 1956. Physical examination was negative except for a 2 cm. lymph node in the left axilla. Tuberculin skin test was positive; all other skin tests were negative. Routine laboratory studies were within normal limits. Roentgenograms of the chest, September 27,

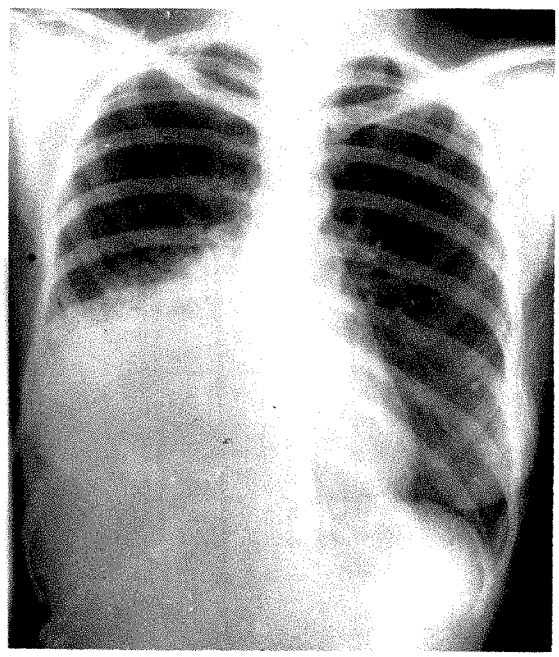

Fig. 1. Case I. Homogeneous consolidation in right lower lung.

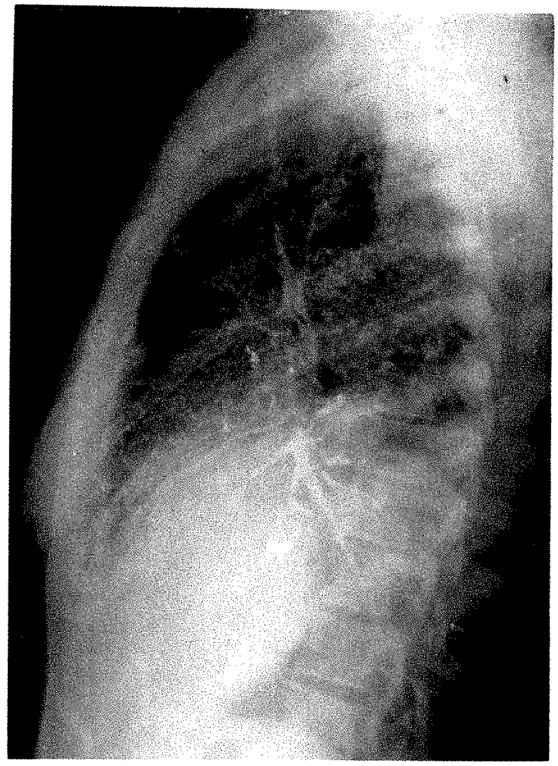

Fig. 2. Case I. Bronchogram showing incomplete filling of the right lower lobe, with tapering of branches, compression and displacement.

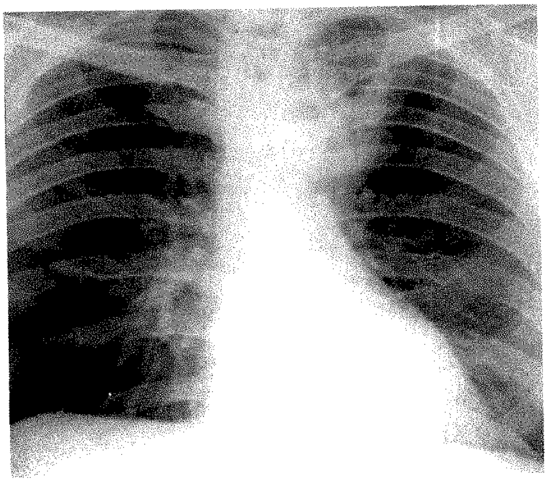

Fig. 3. Case II. Left upper lobe abnormality which did not show any change in eighteen months.

1956, showed a mass in the left upper lobe with a finely irregular margin. Air filled bronchi were visible within the mass (Fig. 4). A bronchogram showed a normal bronchial tree (Fig. 5). A laminagram of the left upper lobe demonstrated the patent bronchi within the mass (Fig. 6). Bronchoscopy was negative and bronchial washings were negative for malignant cells and acid fast bacilli. Excisional biopsy of the left axillary lymph node showed chronic hyperplastic lymphadenitis and no neoplasm.

Thoractomy was performed on December 7, 1956. A moderately firm mass was palpated in the anterior and apical posterior segments of the left upper lobe. It appeared to be adherent to the chest wall and mediastinum. The tumor was dissected away and biopsy of the remaining mediastinum showed no neoplasm. Mediastinal and hilar lymph nodes were not felt to be involved. Microscopic examination revealed a lymphoblastoma of lymphosarcoma type. One lymph node in the hilus showed changes suggestive of early lymphoblastomatous involvement, but the remainder of the lymph nodes were negative.

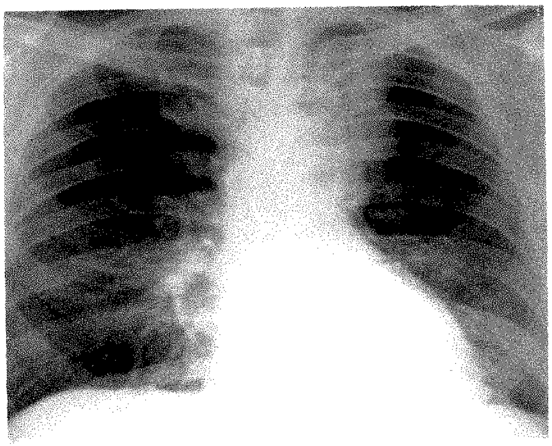

Fig. 4. Case II. Increasing mass in left upper lobe.

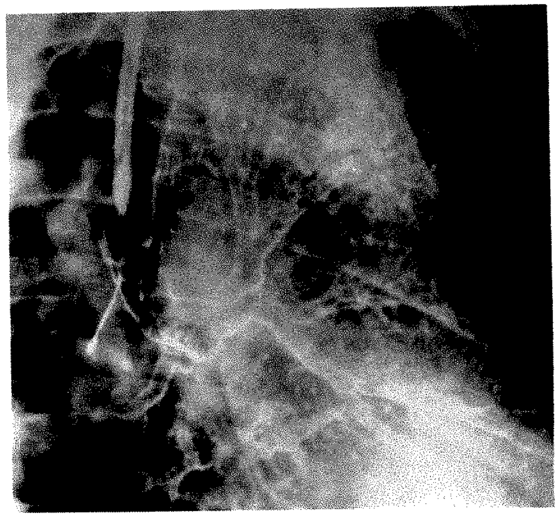

Fig. 5. Case II. No bronchographic abnormality is visualized in the region of the mass.

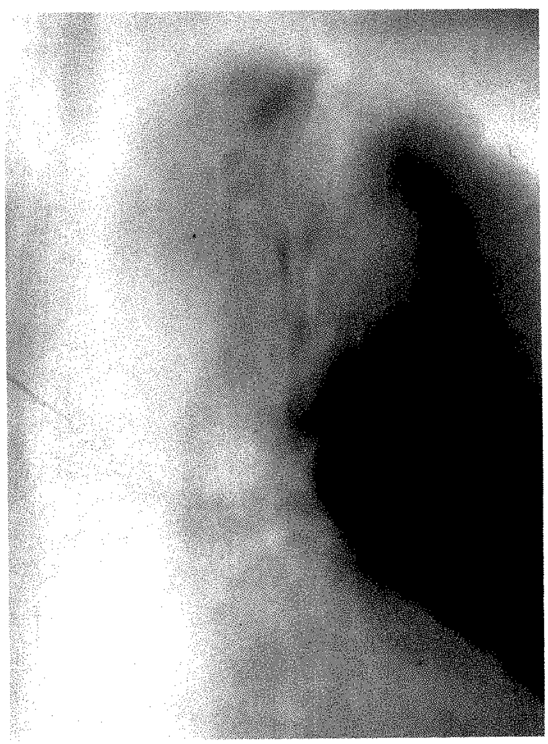

Fig. 6. Case II. Laminagram confirming patent bronchi within the mass.

The patient's postoperative course was uneventful. No radiation therapy was given. At the time of an annual examination, May 13, 1959, he was found to be in excellent condition with no evidence of recurrence of his disease.

Case III. E.V., No. 849-076, a forty-nine year old female, was admitted to University Hospital on August 12, 1956. Eight months prior to this a "spot" on the right lung was noted on a minifilm of the chest during a routine survey. The patient was completely asymptomatic.

Physical examination and routine laboratory studies were negative. All skin tests were negative. Atypical acid fast bacilli were cultured from the sputum. A roentgenogram of the chest (Fig. 7) showed a mass in the hilar portion of the right middle lobe. The margins were poorly demarcated. The hilus was not enlarged and the vessels at the hilus appeared to be normal. The appearance of the chest was identical with that on roentgenograms made elsewhere on January 10, 1956. Bronchoscopy revealed no abnormality except for some slight narrowing of the branches to the right lower lung. Bronchograms were normal. Filling of both segments of the middle lobe was obtained (Fig. 8). Bronchial washings were negative for malignant cells.

On August 21, 1956 a right middle and upper lobectomy was performed. There was fleshy consolidation of the middle lobe and the disease crossed the horizontal fissure to involve the upper lobe. Hilar and mediastinal lymph nodes were not involved. Microscopic examination showed widespread infiltration of both lobes by lymphosarcoma. This was especially heavy around the lesser bronchi. All lymph nodes were negative.

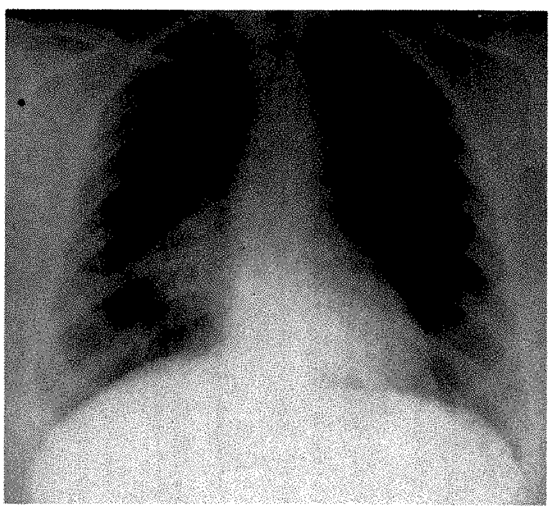

Fig. 7. Case III. Right middle lobe hilar mass which was first seen on a survey roentgenogram.

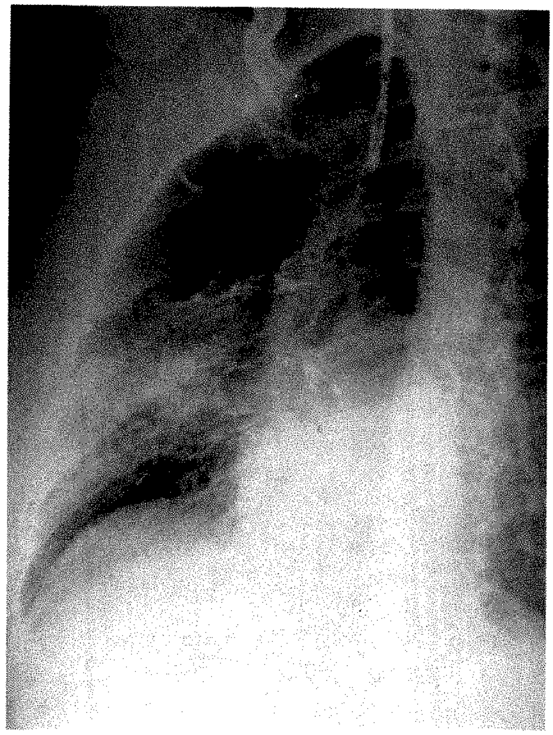

Fig. 8. Case III. Patent bronchi in the area of the mass.

The patient received postoperative irradiation elsewhere and was last heard from on May 1, 1959 at which time she was well.

Case IV. N.G., No. 132-866, a fifty-six year old female, gave a history of having had pleurisy in 1937. In 1943 she had had pneumonia and pleurisy in the left lung and in 1944 pneumonia in the right lung. Since that time she had been bothered with numerous "chest colds." In November, 1955, a mobile survey roentgenogram revealed changes of bilateral apical tuberculosis. She was hospitalized, treated with INH and PAS with rapid clearing of the lesions and was discharged in August, 1956. About eight months later, she noted the onset of dyspnea on exertion and a feeling of tightness in her chest. A roentgenogram revealed a lesion in the right lung. Repeat examination one month later was reported to show an increase in the size of this lesion. She was

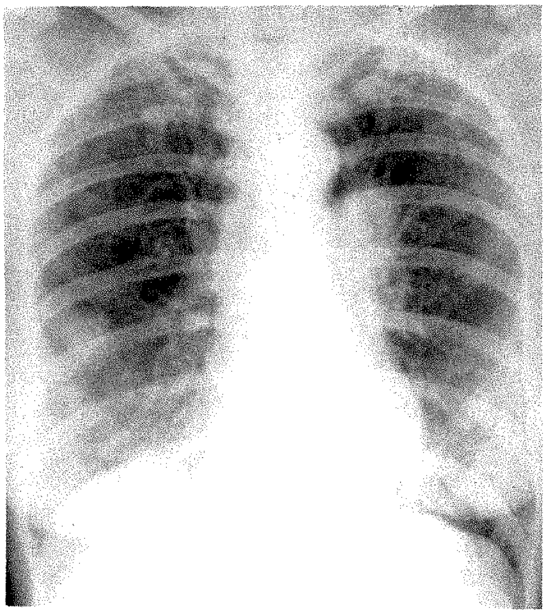

Fig. 9. Case iv. Left hilar mass and excavated nodule in right middle lobe.

admitted to University Hospital on May 19, 1957.

Positive physical findings were limited to the chest. Routine laboratory studies were negative except for a hemoglobin of 11.5 gm. A roentgenogram of the chest on May 17, 1957 (Fig. 9) revealed a mass extending into the left upper lobe from the hilus. A second mass was present in the peripheral portion of the right middle lobe. This second lesion appeared to be cavitary. Bilateral apical pleural scarring was present. On laminagrams (Fig. 10, *A* and *B*) the left upper lobe lesion could not be separated from the hilus, although it appeared to involve lung parenchyma. Enlarged lymph nodes were not identified. Air filled bronchi could be seen within the mass. A cavity was definitely present in the right lung lesion. Left scalene lymph node biopsy revealed only hyperplastic lymph nodes and no neoplasm. On May 31, 1957, the patient was bronchoscoped. Using the right angle lens, the orifice of the left upper lobe bronchus appeared to be re-

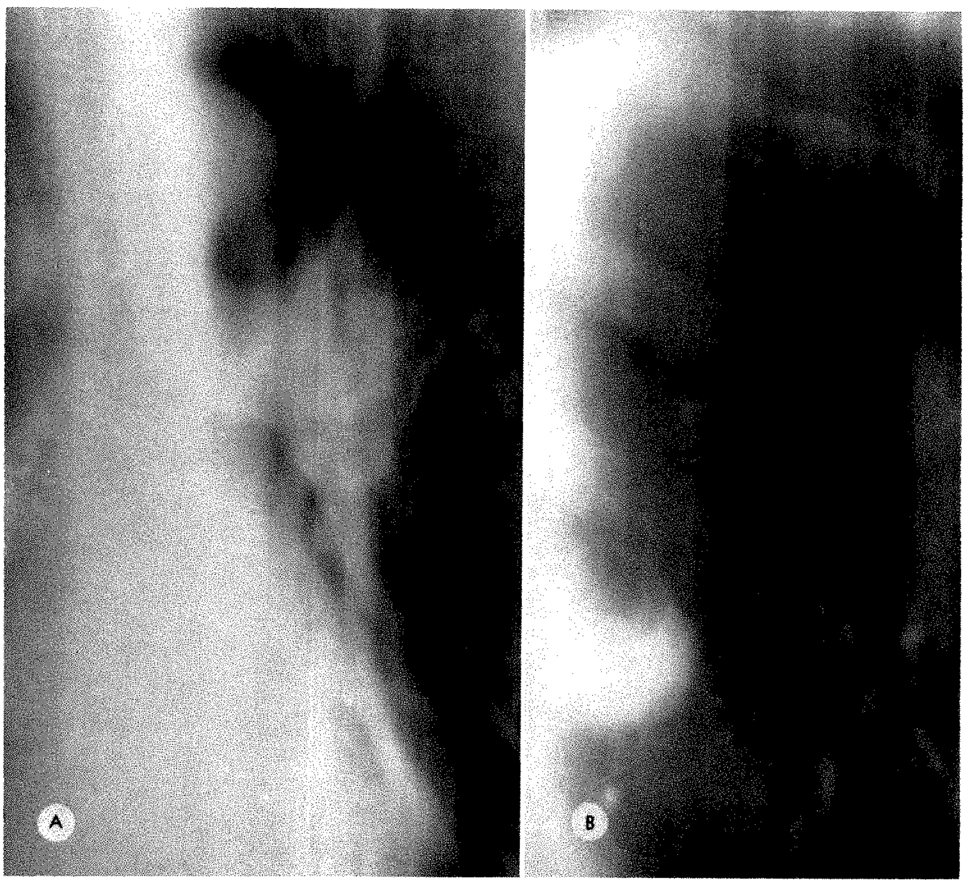

Fig. 10. Case iv. (*A*) Laminagram through the left hilar mass. (*B*) Laminagram through the right middle lobe showing excavated nodule.

duced to a slit. The mucosa appeared normal and the narrowing was thought to be due to extrinsic pressure. Biopsy of the mucosa near this bronchial orifice was reported as showing two small collections of markedly hyperchromatic cells which raised the possibility of carcinoma, although this diagnosis could not be definitely made.

Right thoracotomy was done on June 3, 1957. A rounded, somewhat soft lesion, 2.5 cm. in diameter, was found in the right middle lobe. The pleura overlying the lesion was grayish-white in color. A wedge resection was performed. Microscopic examination revealed lymphosarcoma.

The patient was given postoperative radiation therapy. Anterior and posterior right and left chest fields were used, each field measuring 14×11 cm. The factors were: 220 kv., half value layer 1.5 mm. copper and focus skin distance 50 cm. A dose of 1,625 r measured in air was delivered to each field over twenty-six days. There was a marked decrease in the size of the left hilar lesion following irradiation. Clinically, the patient was definitely improved. Three months later she began to notice some shortness of breath and substernal discomfort. Roentgenograms of the chest showed bilateral parenchymal abnormality and a second course of radiation therapy was administered, 1,200 r in air being delivered to each of the four chest fields. There was slight improvement in symptoms following this. One month later she began to vomit and her condition deteriorated appreciably.

On December 12, 1957 she was re-admitted to this hospital with severe dyspnea at rest and a temperature of 103°F. She complained of intermittent chest pain and cough productive of a thick, mucoid sputum. There was no hemoptysis and no clubbing of the fingers. A chest roentgenogram made at this time (Fig. 11) revealed an increase in the size and extent of the bilateral parenchymal infiltrations since the previous roentgenogram made two months before. She was given a course of intravenous nitrogen mustard with minimal relief from her symptoms. The patient died on January 26, 1958. An autopsy was not performed.

Case v. B.L., No. 786-529, a fifty-seven year old male, was admitted to University Hospital on June 6, 1954. In February, 1953 he "caught a cold" and noted chills and fever and ease of fatigue. It was felt that he had lobar pneumonia and pleurisy, and he was treated

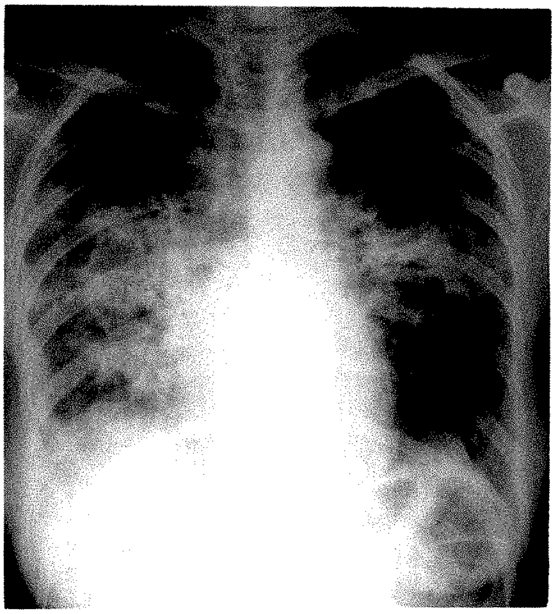

Fig. 11. Case iv. Extensive bilateral spread found five months after irradiation.

with penicillin and streptomycin with relief of his symptoms. Review of a chest roentgenogram made at that time showed a large left pleural effusion obscuring the lower left lung and displacing the mediastinum to the right. One month following treatment, he began to notice ease of fatigue and some shortness of breath. Thoracentesis was performed three times and fluid was removed at each tapping. In August, 1953, because of increase of his symptoms he was hospitalized elsewhere for six months. He was finally advised to have an operation which he refused. He went back to work but was forced to return to a hospital because of his extreme weakness.

Physical findings were limited to the lungs. Routine laboratory tests and skin tests were negative. A roentgenogram of the chest on admission (Fig. 12) showed a large, hemispherical mass with an irregular margin in the posterobasal segment of the left lower lobe. On lateral projection the posterior costophrenic sulcus was obliterated. In view of the previous roentgenograms, this was thought to represent a loculated pleural effusion. Thoracentesis was performed on the following day and 300 cc. of serosanguineous fluid was removed. Chest roentgenograms following the tapping showed no change in the appearance of the mass.

On June 28, 1954 a thoracotomy was done with the object of draining the empyema. A 6 cm. incision was made along the left tenth

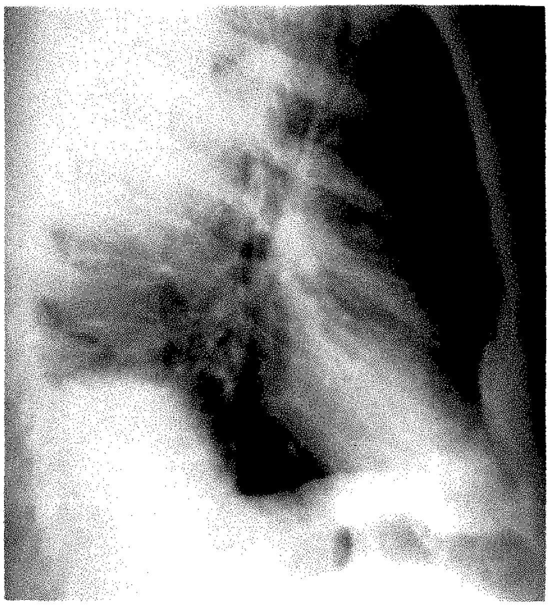

FIG. 12. Case v. Large mass found at left base posteriorly.

rib posteriorly and a portion of the rib was removed. The parietal pleura in the region was 1 to 2 cm. thick and shaggy but not fibrotic. In the pleural space 300–500 cc. of turbid fluid was found. Finger palpation of the lung that fitted into the mediastinal portion of the posterior costophrenic sulcus showed it to be firm and to contain less air than the lung laterally. It was felt that this was due to the prolonged collapse of the lung. A rubber drain was placed in the costophrenic sulcus and the chest was closed. Microscopic examination of the pleural fluid revealed leukocytes, fibrin and serosal lining cells, but no malignancy. Operative biopsy of the pleura showed heavy subpleural infiltrates. There was no evidence of inflammatory reaction on the pleural surfaces. The patient did well postoperatively and was discharged, the diagnosis being sterile empyema following antibiotic therapy.

In August, 1954 a follow-up examination showed some increase in the size of the mass on chest roentgenograms. There also appeared to be some abnormality in the lingular portion of the left upper lobe. A bronchogram showed incomplete filling of the posterobasal branches with shortening and tapering of these bronchi (Fig. 13*A*). Bronchoscopy was negative. The patient's chest was tapped posteriorly and 4 cc. of straw colored fluid was obtained. An operation was advised but the patient refused.

He was well until May, 1957 when, following an upper respiratory infection, he noted some shortness of breath and a cough productive of grayish sputum which was occasionally streaked with blood. He was re-admitted to the hospital. Physical examination revealed no lymphadenopathy; the liver and spleen were not palpable. Chest roentgenograms showed considerable increase in the size of the mass and a left pleural effusion was present. On September 24, 850 cc. of fluid was removed from the left pleural space. Microscopic examination was negative for malignant cells. A left scalene fat pad biopsy showed reticuloendothelial hyperplasia of the lymph nodes but no malignancy. Bronchograms made at this time demonstrated the increase in the size of the pulmonary lesion and further shortening, tapering and displacement of the bronchi when compared with the examination three years previously. The disease process appeared to involve the peripheral bronchi initially, then proceeded towards the hilus (Fig. 13*B*).

Thoracotomy was done on October 10, 1957. On entering the thoracic space it was noted that the lower lobe was completely adherent to the parietal wall. Over the lingula anteriorly were only a few adhesions. The lower lobe was represented by a bulky mass of firm tissue and even an extrapleural plane could not be established. The mass was freed by finger dissection. A left lower lobectomy was performed. Several enlarged lymph nodes were found near the hilus. Examination of the removed lobe showed it to be filled with 1–2 cm. of tan colored, rubbery nodules which became confluent in places. One large mass, measuring 21 × 14 cm. was composed of this tissue, which microscopically was lymphocarcoma with extensive invasion of the peribronchial tissues and interalveolar septa. Then neoplasm extended along the major lobar bronchus and almost completely infiltrated its wall. The removed lymph nodes were all involved.

The patient had several complications arising from the surgery and required numerous thoracenteses, all of which were negative for malignant cells. He had several episodes of hemoptysis immediately after the operation. Postoperative irradiation was given through 15 × 12 cm. anterior and posterior left chest fields. The factors were 220 kv., half value layer 1.5 mm. Cu and a focus skin distance of 50 cm. A total of 1,875 r in air was given to each

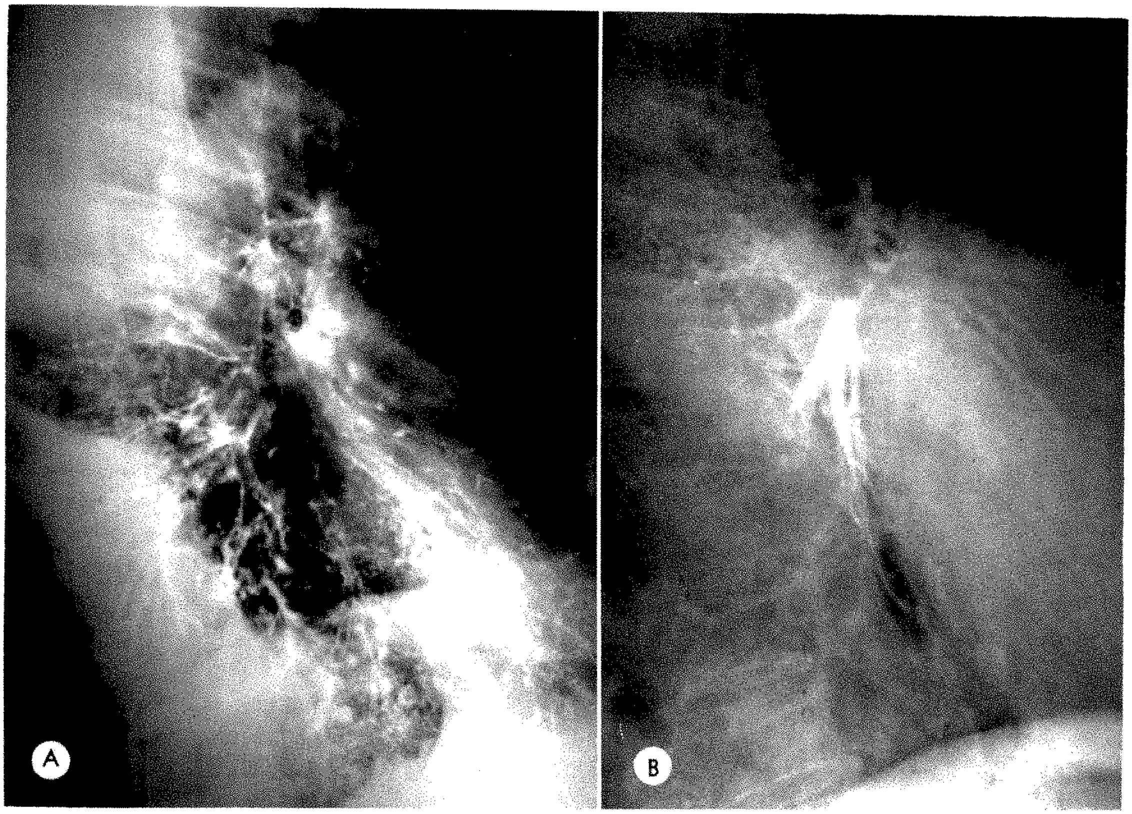

Fig. 13. Case v. (*A*) Bronchogram showing patency of bronchi in region of mass. (*B*) Increase in mass over three year period with further tapering and displacement of bronchi.

field over a period of eighteen days. The patient was last heard from in March, 1959, at which time he was well.

CLINICAL FEATURES

In 39 cases of primary pulmonary lymphosarcoma, 5 of which are reported here and 34 collected from the literature, the average age at the time of diagnosis was 51.9 years, the range being from thirty-four to seventy-five years. There were 16 males and 22 females, a ratio of about 3:4. Three of this group were Negroes, the remainder were Caucasians.

There is no definite symptom complex associated with this disease. Almost one-third of the patients were completely asymptomatic, the pulmonary lesion first being detected on survey chest roentgenograms or at the time of examination for complaints not referable to the respiratory tract. The most common symptom was cough usually productive of small amounts of mucoid sputum. This was present in 23 of 38 patients. Hemoptysis occurred in 6 cases and was in the form of pinkish or blood streaked sputum. Massive hemoptysis was not encountered. Chest pain usually localized to the side of the lesion was noted by 11 patients. This was generally of an aching nature; the pleuritic-type pain being less common. Three patients were first seen because of pain in the shoulder and in each case the lesion was in the upper lobe on the same side.

Physical examination, except for findings related to the chest, was negative. If lymphadenopathy, hepatomegaly or splenomegaly are present, the pulmonary involvement is most likely secondary to generalized lymphosarcomatosis. Two patients had clubbing of the fingers. In a case described by Cooley *et al.*,[5] the lesion had a large central cavity and pleural effusion

was present, while in our Case I there was a previous history of pneumonia and pleurisy. It is felt that the clubbing is not due to the lymphosarcoma *per se*, but to the accompanying infection.

A history of recurrent episodes of pneumonitis or upper respiratory tract infections was definitely more common among the patients with pulmonary lymphosarcoma than would be expected in the average population.

Routine laboratory studies are generally normal. An occasional patient may have a moderately low hemoglobin or elevated erythrocyte sedimentation rate, but these are of no diagnostic value.

PATHOLOGY

There is abundant lymphoid tissue in the normal lung. The bronchial mucosa is infiltrated with lymphocytes and may contain lymphoid follicles. Lymphoid tissue extends as far peripherally as the alveolar ducts. Accumulations of lymphocytes and lymph channels are present in the adventitia of the arteries and veins in the lung, in the pleura and interlobar connective tissue.[18] As with lymphoid tissue elsewhere in the body, these foci may undergo lymphosarcomatous change.

Lymphosarcoma in the lung is essentially an infiltrative process. The principal mode of spread of the tumor is by contiguous growth. The peribronchial lymphoid tissue is commonly involved, but the tumor tends to grow away from, rather than into, the bronchial lumen. The malignant cells may penetrate almost the entire thickness of the bronchial wall, in some cases destroying the bronchial cartilages;[11] submucosal collections of lymphosarcoma cells are commonly seen, but it is rare for the bronchial mucosa to be ulcerated. Such ulceration was found in 4 of the 39 cases and in only one of these (Hall and Blades,[12] Case I) was there sufficient intrabronchial growth to produce obstruction. The blood vessels are affected in a like manner. In almost every case report, the patency of the bronchi and blood vessels within the tumor is commented on.

As the tumor infiltrates the interalveolar septa, the cellular accumulation produces marked thickening of these structures. Eventually, adjacent septa become so swollen that the alveolar air space between them is obliterated. It is extremely uncommon to find free lymphosarcoma cells within a recognizable alveolus. As the disease progresses, there is gradual loss of the pulmonary architecture so that in the more advanced stages the tumor appears to consist solely of lymphosarcomatous elements, the normal pulmonary tissue having been completely destroyed.

The tumor is not encapsulated although a rim of compressed normal lung may surround it. Microscopically, the borders of the tumor are not distinct because of the multiple small extensions of malignant cells into the adjacent septa. The pleura seems to offer no barrier to the growth of the lymphosarcoma, and contiguous lobes and pleural surfaces are usually involved.

Metastases probably occur late in the course of the disease and may represent hematogenous or lymphogenous spread. The most common site of secondary involvement is the hilar and mediastinal lymph nodes. Cases have been reported of metastases to the skull,[12] spine,[12] ribs,[12,21] liver,[21] lung,[4,17,30] submaxillary gland,[4] and parotid gland.[16] In our Case V it is felt that the cavitary lesion in the right lung probably represented a metastasis and the bilateral pulmonary disease leading to the patient's death was most likely spread of lymphosarcoma.

Two cases have been reported which possibly represent multiple primary sites in the same patient. In the case of Beck and Reganis,[3] two years following lobectomy for primary lymphosarcoma of the lung, gastroscopic diagnosis of lymphosarcoma of the stomach was made and a gastric resection performed. The patient was last reported well and without evidence of disease five and one-half years following lobectomy. The patient reported by Justin-Besancon *et al.*[16] originally had bilateral lymphosarcoma of the lung which was

treated by radiation therapy. She did well for five years and then developed an antral ulcer which was found to be lymphosarcomatous at the time of gastrectomy. Subsequently, she had involvement of the ileum and recurrence of the sarcoma in the lung and died eight years after the original diagnosis was made.

The microscopic pathology of primary lymphosarcoma in the lung is identical with that of generalized lymphosarcoma. In most of the cases, the tumor was composed of mature lymphocytes with few mitoses being seen. In a few of the cases, the cells appeared to be less mature and were described as lymphoblasts.

BRONCHOSCOPIC FINDINGS

Bronchoscopic findings are known in 29 cases. In 12 they were completely normal. In one case an ulcerating lesion was seen which proved to be lymphosarcoma by biopsy. In a second case, biopsy of an intact friable mucosa revealed a collection of malignant cells submucosally which were felt to represent either small cell anaplastic carcinoma or lymphosarcoma. These are the only 2 cases in which the correct diagnosis was made preoperatively. Some mucosal abnormality in the region of the bronchus from the involved lobe was found in 6 other patients. This generally was an area of granularity or edema and hyperemia. In most of these, biopsy revealed only inflammatory tissue. Nine cases showed evidence of extrinsic pressure on a bronchus without mucosal involvement.

Examination of the sputum and bronchial washings were negative in 11 of the 14 cases in which it was reported. In 3 cases, malignant cells were found, but their type could not be identified.

ROENTGEN FINDINGS

Primary lymphosarcoma of the lung appears on chest roentgenograms as a homogeneous mass, often occupying an entire lobe. There is no apparent predilection as to the lobe involved: 11 of 39 cases were in the left upper lobe, 9 in the right lower lobe, 6 in the left lower lobe, 6 in the right upper lobe and 3 in the right middle lobe. Four cases showed bilateral lung involvement at the time the diagnosis was made. In all cases the mass was sizable when first detected, the smallest lesion being 3 cm. in diameter. The tumor tends to develop in the hilar portion of the lobe rather than peripherally, probably because of the greater concentration of lymphoid tissue around the larger bronchi.

On roentgenograms the mass is usually well demarcated from normal lung, although its margins are somewhat hazy and irregular because of small extensions into the surrounding alveolar septa. As obstruction of the major bronchi almost never occurs; significant atelectasis is rarely seen. The infiltration and enlargement of the interalveolar septa with obliteration of the alveoli produce the roentgen picture of consolidation with minimal, if any, loss of lung volume. The bronchi remain patent and traverse the mass so that in some cases an air bronchogram may be seen (Fig. 5, 8, and 13*A*).

Pleural involvement was commonly noted at the time of thoracotomy in our patients, the lymphosarcoma fusing the visceral and parietal layers. Despite this, pleural effusion in these cases is rare. Such an effusion was present in one of our patients (Case V) and in 3 reported in the literature. Microscopic examination of the fluid revealed malignant cells in only one case (Sternberg *et al.*,[30] Case 6).

In only one of the reported cases has the lesion shown some suggestion of calcification within the mass (Grimes *et al.*,[11] Case 2). In 3 of the remaining 38 cases there was cavitation within the tumor. Case 3 in the series of Sternberg *et al.*[30] had a cavity measuring 7 cm. in diameter, the walls being formed by necrotic tumor tissue. A smooth-walled cavity, 8 cm. in diameter, was present in Case 5 reported by Cooley *et al.*[5] There was a smaller cavity in the right lung lesion in Case IV of our series (Fig. 10*B*). In one case, multiple small bronchiectatic cavities were found within

the mass on pathologic examination.[29] Because of the frequent respiratory infections, pneumonic changes in the lungs may obscure the underlying neoplasm, which will then become evident following treatment with antibiotics. Hilar or mediastinal lymphadenopathy was not present roentgenographically in any of the cases.

Information concerning bronchography is available in 9 cases. Three were normal and one showed incomplete filling of the bronchi of the involved lobe. In the remainder there were distortion and compression of the segmental bronchi, giving them a tapered appearance in the region of the tumor. Involvement of the bronchi begins in the smaller peripheral branches and proceeds centrally (Figs. 13, *A* and *B*). Even when the mass becomes large enough to displace and stretch the bronchi, significant bronchostenosis and atelectasis are rare. In one case,[27] submucosal collections of lymphosarcoma cells produced an irregularity in the contour of the bronchi on the bronchogram that was suggestive of the changes of chronic bronchitis.

DIFERENTIAL DIAGNOSIS

The preoperative diagnosis in most cases of pulmonary lymphosarcoma was bronchogenic carcinoma. The roentgen findings, particularly if bronchography is performed, show some differential points. The lymphosarcomata in this series were all large when first detected and most of them were in the hilar portion of a lobe. It would be extremely rare for a bronchogenic carcinoma in this location to attain such size without obstructing the bronchus and producing distal atelectasis. Wilt *et al.*[38] reviewed the bronchograms of 236 patients with bronchogenic carcinoma of all types. A bronchial block was demonstrated in almost 90 per cent of the patients, and in 213 cases the bronchogram was considered to be diagnostic of carcinoma. The clinical features of the two diseases are considerably different in most cases. Bronchogenic carcinoma usually grows more rapidly, hemoptysis is a more constant and striking feature, and histologic examination of the sputum will often show malignant cells of a specific nature.

Solitary pulmonary lesions do occur in generalized lymphosarcomatosis. Atelectasis distal to the lesion is rarely encountered and major bronchostenosis will be the exception to the rule. The distinction between primary and secondary involvement of the lungs depends on the presence or absence of lymphosarcoma elsewhere in the body. In most cases this cannot be definitely determined except at the time of autopsy or if there is long-term survival following local treatment of the pulmonary lesion.

Alveolar cell carcinoma arises in the terminal bronchiolar or alveolar epithelium and produces a true consolidation of lung by filling the alveoli with tumor cells. This can present on chest roentgenograms as a solitary mass which may be indistinguishable from lymphosarcoma. In some cases bronchograms will show evidence of a block, but in others the bronchogram will be normal. Over 70 per cent of patients with alveolar cell carcinoma will complain of cough and in an appreciable number this will be productive of a glairy, mucoid sputum. Only 7 in a series of 154 patients were asymptomatic.[31] Papanicolaou[19] has noted that this tumor exfoliates freely and abundant cells may be recovered from the sputum that are characteristic of this type of neoplasm. Watson and Smith[36] studied the sputum of 15 patients with alveolar cell carcinoma. Malignant cells were found in 9 cases and cells strongly suggestive of cancer in another 3. Roelson *et al.*[24] found positive sputa in 5 of 8 patients studied.

Lobar pneumonia produces consolidation without atelectasis, but the acute clinical history and symptoms are characteristic and it is unlikely that this would be confused with lymphosarcoma. This is not true in the cases of chronic pneumonitis such as lipoid pneumonia. The most common roentgen finding in lipoid pneumonia is that of bilateral interstitial pneumonitis. Occasionally, the disease may be localized

and appear as a single mass on chest roentgenograms. The right middle and lower lobes are the most common sites of involvement. The usual bronchographic findings show obstruction of the terminal bronchioles[13] not unlike that seen with primary pulmonary lymphosarcoma. In the exceptional case, blockage of a major bronchus may occur with lobar atelectasis. In the majority of patients, a history of chronic oil ingestion will be obtained and, in some, intracellular oil in the desquamated cells in the sputum will be demonstrated. Hall and Blades[12] report the use of a trial of irradiation to differentiate lipoid pneumonia from lymphosarcoma.

Pulmonary infarction produces an area of consolidation because of the outpouring of fluid and cells into the alveoli. Infarcts may reduce the lung volume, but atelectasis is not a prominent feature. A history of sudden chest pain, hemoptysis and shortness of breath are characteristic but not present in all cases. Roentgenograms of the chest made over a period of several weeks will differentiate this from primary lymphosarcoma. An infarct always extends to at least one, and often two, pleural surfaces; pleural effusion occurs in 13 to 40 per cent of pulmonary infarctions;[14] serial examinations will show diminution in the size of the infarct as it is organized and absorbed.

TREATMENT AND PROGNOSIS

Two of the 38 patients about whom information is available received no therapy, since the diagnosis of lymphosarcoma was made at the time of autopsy.[21,33] Four patients were considered to be inoperable because of the local extent of their disease. There was no evidence of distant metastases in any of these patients. All were treated by irradiation alone. Two died of metastatic lymphosarcoma within two years (Hall and Blades,[12] Case I and 3), one died of recurrent lymphosarcoma in the lungs eight years after treatment,[16] and one patient, our Case I, is living and well nine years and ten months after therapy.

Pneumonectomy was performed in 13 cases with one death due to postoperative complications. Three of these patients received postoperative irradiation: 2 are alive and well but have been followed for less than five years (Grimes *et al.*,[11] Case 1; and Cooley *et al.*,[5] Case 3), and the third died fourteen years postoperatively without postmortem examination. Of the 9 patients treated by pneumonectomy only, 5 died within five years, 4 presumably from their lymphosarcoma (Van Hazel and Jensik,[34] Case 1; Sternberg *et al.*,[30] Case 4; Cooley *et al.*,[5] Case 5; and Weissman and Christie[37]). The fifth patient was autopsied and no evidence of lymphosarcoma was found (Rose,[25] Case 2). One patient is alive and has been followed for less than five years,[2] 2 are alive at six and seven years respectively (Hall and Blades,[12] Case 2; and Grimes *et al.*,[11] Case 2), and the last patient had two recurrences in the lung treated by irradiation. He died of coronary occlusion thirteen years and nine months after treatment.[17]

Eighteen patients had one or two lobes removed. One patient died five weeks postoperatively from a cerebrovascular accident.[26] Seven of these patients had postoperative irradiation: 5 are alive and well less than five years (Cooley *et al.*,[5] Case 1; Ergin and Kemler;[7] Sternberg *et al.*,[30] Case 5; authors' Case III; and authors' Case V), one is alive at eight and one-half years with known disease in the lung and hilar lymph nodes[4] and the seventh patient has had several additional courses of radiation therapy and is alive at twelve years.[39] Of the remaining 11 patients, one died three and one-half years postoperatively from tuberculosis, the status of his lymphoma not being known (Sternberg *et al.*,[30] Case 3). Five patients are alive less than five years (Rose,[25] Case 1; Spatt and Grayzel;[29] Sternberg *et al.*,[30] Case 5; and Van Hazel and Jensik,[34] Case 3 and 7), and 5 are alive from five to ten years (Schulze;[27] Van Hazel and Jensik,[34] Case 4; Beck and Reganis;[3] Anlyan *et al.*;[1] and authors' Case II). One of these patients developed a hilar mass four years after lobectomy which was irra-

diated,[1] and a second has known disease in the lung and hilar lymph nodes at eight and one-half years.[4]

Case IV in this report had one lesion removed by wedge resection and a second treated with irradiation. She died five months postoperatively.

COMMENT

Primary lymphosarcoma of the lung is a slow growing tumor and widespread dissemination is uncommon. Two patients (authors' Case III; and Schulze[27]) had been observed for five years without treatment before surgery. In both cases, the lesions enlarged slightly over this period. Lobectomy was performed and both are alive and well two and one-half years after operation. The mistake in each case, leading to the delay in treatment, was to consider the lesion nonmalignant because of the patent bronchi within the mass.

Bronchoscopy has not been of much assistance in establishing the diagnosis preoperatively. It has been shown in cases of bronchogenic carcinoma that biopsy of normal appearing mucosa may reveal submucosal infiltration by malignant cells.[22] As lymphosarcoma is frequently found beneath the bronchial mucosa, it is possible that blind biopsies of the bronchus leading to the involved segment may contribute more positive findings.

Chest roentgenograms may be misleading when attempting to assess the extent of lung involvement. In many of the cases adjacent lobes, pleura or mediastinum have been involved, although the lesion appeared on roentgenograms to be a fairly well localized mass. Robbins[23] has noted that at times the pathologist finds lymphomatous foci in the lung as large as 1 cm. in diameter which were not seen on roentgenograms. When the hilar or mediastinal lymph nodes are involved, they are usually not sufficiently enlarged to be recognized roentgenologically.

Adequate follow-up of a sufficient number of cases is not available to enable us to evaluate the various forms of treatment. At present, the definite diagnosis of lymphosarcoma is generally made at the time of thoracotomy. If the lesion is considered resectable, lobectomy or pneumonectomy seems to be the reasonable mode of treatment. However, because of the microscopic spread of the tumor, the inability of the surgeon to always recognize lymph node involvement (our Case II), and the radiosensitivity of lymphosarcoma, postoperative irradiation of the lung and mediastinum seems to be indicated.

SUMMARY

1. Primary lymphosarcoma of lung is a relatively rare lesion presenting as a mass in the lung, but is a distinct entity with some characteristic roentgen findings which are of diagnostic value.

2. Five new cases, histologically proved, are added to the 34 cases previously reported in the literature.

3. Approximately one-third of the 39 patients discussed had no symptoms. In the remaining two-thirds, cough, hemoptysis and chest discomfort were the most frequent findings. Recurrent pneumonitis was common.

4. Bronchoscopy was normal in 12 of 29 cases. Extrinsic pressure, granularity with inflammatory changes, friable mucosa or ulceration may be seen. Biopsy of apparently normal mucosa in the involved segment is suggested to find possible submucosal involvement in a greater number of cases.

5. Sputum and bronchial washings were negative for malignant cells in 11 of 14 cases so studied.

6. Roentgen findings are a homogeneous mass, more centrally than peripherally located, without hilar or mediastinal involvement, and possibly showing slow growth if observed over a long period of time. Atelectasis is rare; patent bronchi may be demonstrated by the "air bronchogram" or by contrast bronchography.

7. The roentgen appearance and clinical course frequently can be differentiated from those of bronchial carcinoma, alveolar

cell carcinoma, lobar pneumonia, lipoid pneumonia and pulmonary infarction.

8. Pulmonary resection, if feasible, with postoperative irradiation, and primary irradiation if thoracotomy demonstrates nonresectability, constitute the treatments of choice.

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ACCESSORY DIAPHRAGM

A CASE REPORT

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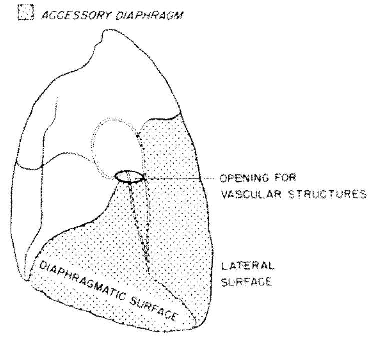
An accessory diaphragm, a rare anomaly, consists of a second leaf of diaphragm which is located in the right chest cavity and separates all or part of the lower lobe from the remaining lung. Two cases have been reported in the current medical literature,[2,3] and we are adding a third case.

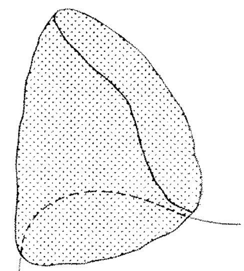
REPORT OF A CASE

A fifty-seven year old white woman died from ascending pyelonephritis resulting from ureteral obstruction by scar tissue twenty-one years after a squamous cell carcinoma of the cervix had been treated by radium.

As a wholly unrelated finding, an accessory diaphragm was found in the right hemithorax. This diaphragm was situated in the oblique fissure and formed a posterolateral pouch in which the right lower lobe was contained. Its insertions were medially the pericardium; anteriorly the diaphragm, about 3–4 cm. from its anterior insertion; laterally the chest wall starting at the level of the seventh rib, and posteriorly the chest wall at the level of the fifth rib near the spine. Its course followed the oblique fissure, thus it had formed a posterolateral pouch in the right thoracic cavity (Fig. 1, *A* and *B*).



A MEDIASTINAL SURFACES OF RIGHT LUNG



B LATERAL VIEW OF LOWER LOBE OF RIGHT LUNG

Fig. 1. (*A* and *B*) Diagrams of the accessory diaphragm and its relation to the right lung.

The bronchovascular elements were normal in their origin and distribution. However, those to the right lower lobe passed through the accessory diaphragm by way of a 2×3 cm. semilunar opening located near the mediastinum. The leaf was composed of connective tissue 1 mm. thick except at the rim of the mediastinal opening where it was approximately 2–3 mm. thick and contained skeletal muscle all along the free edge. The true diaphragm showed normal structure, location and attachment.

In addition to this diaphragmatic anomaly, the right lung showed minor abnormalities. Two supernumerary lobes, about 2.5 cm. in length, arose from the apex of the right lower lobe and were incompletely separated from the lower lobe by shallow fissures. The right lower lobe did not show any bronchiectasis, fibrosis or other pathologic findings. The left lung was not remarkable.

Roentgenographically, the right diaphragm was elevated and the oblique fissure was accentuated and thickened (Fig. 2, *A* and *B*). Anteriorly, the right diaphragm was about 4.5 cm. higher than the left. The contour of the diaphragm was regular. The oblique fissure was shown clearly as a band-like soft tissue shadow between the fifth and sixth ribs in the intercostal space. Anterolaterally, the same fissure was seen as a linear density at the upper margin of the fourth rib.

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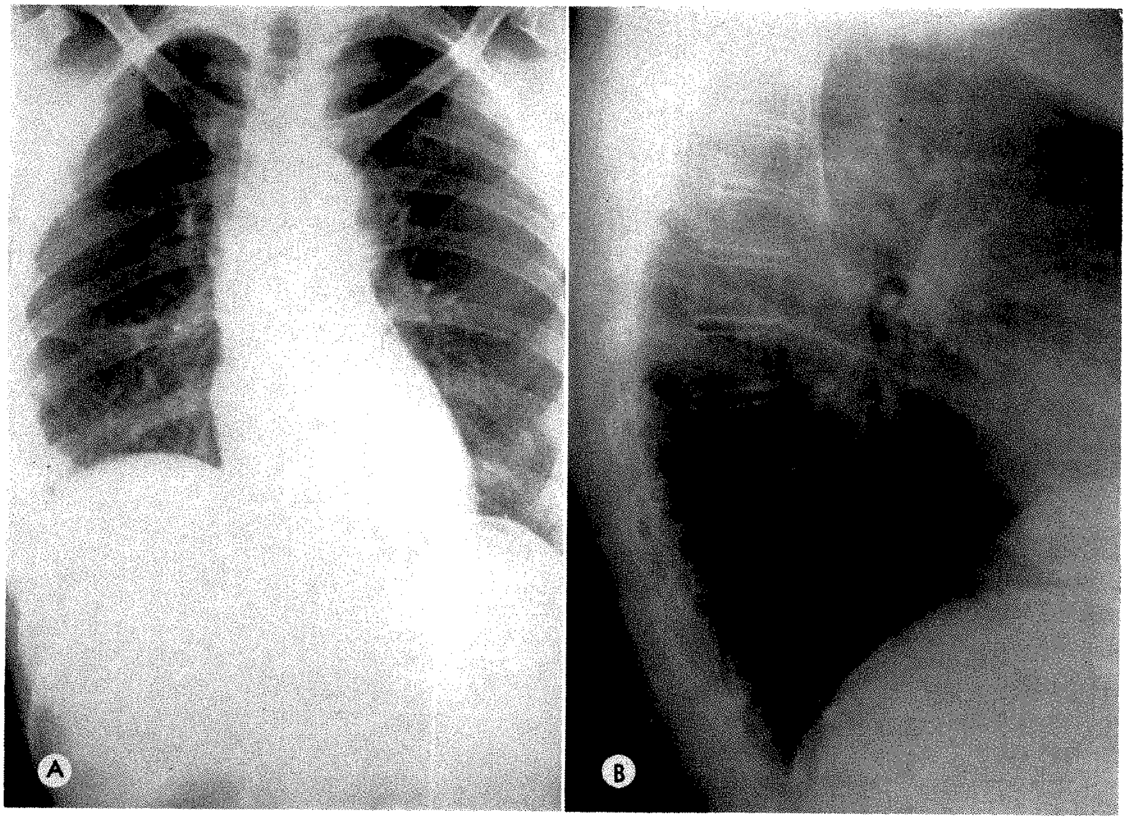

FIG. 2. (*A* and *B*) Posteroanterior and lateral roentgenograms showing elevation of the right diaphragm and thickening of the oblique fissure.

DISCUSSION

For a roentgenologic differential diagnosis, the findings of an elevation of the right diaphragm and thickening of the oblique fissure without evidence of any other lesion in the right chest indicate that an accessory diaphragm must be considered, especially when the patient has been followed for a long period of time without any change in the roentgenographic appearance.

We have been able to find two reports in the literature that give findings with minor differences but similar to those presented in this report. Drake and Lynch[2] discussed the case of a twenty-six year old male where only a small part of the right lower lobe was found in the pouch formed by the accessory diaphragm. In the patient of Sappington and Daniel,[3] a seven year old girl, an accessory diaphragm separated the right lower lobe from the upper lobe, as was noted in our patient.

It is noteworthy that, in the 2 reported cases, bronchiectasis of the right lower lobe led to lobectomy. Our patient, on the other hand, showed only supernumerary lobes. The absence of bronchiectasis in our case may be explained by the anatomic findings; the accessory diaphram was composed of fibrous tissue and very little muscle. In the previous reports, both patients had accessory diaphragms that were muscular. Contraction of the muscle probably caused incomplete aeration and intermittent obstruction of the bronchioles with resulting infection and bronchiectasis. Since little or no muscle was present in the accessory diaphragm of our patient, this mechanism did not function.

A case reported by Allen[1] was related,

but not similar, to our case. It consisted of transpleural muscles between the sixth rib and the central tendinous part of the right diaphragm, situated in the oblique fissure. This represents an incomplete but muscular accessory diaphragm.

SUMMARY

A case of accessory diaphragm is reported in a fifty-seven year old white female. It consisted of a fibrous membrane separating the right lower lobe from the rest of the lung. Its roentgenologic appearance is briefly discussed.

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HORIZONTAL LAMINAGRAPHY: A SUPPLEMENTAL DIAGNOSTIC METHOD IN TUMORS OF THE LUNG, ESOPHAGUS AND MEDIASTINUM*

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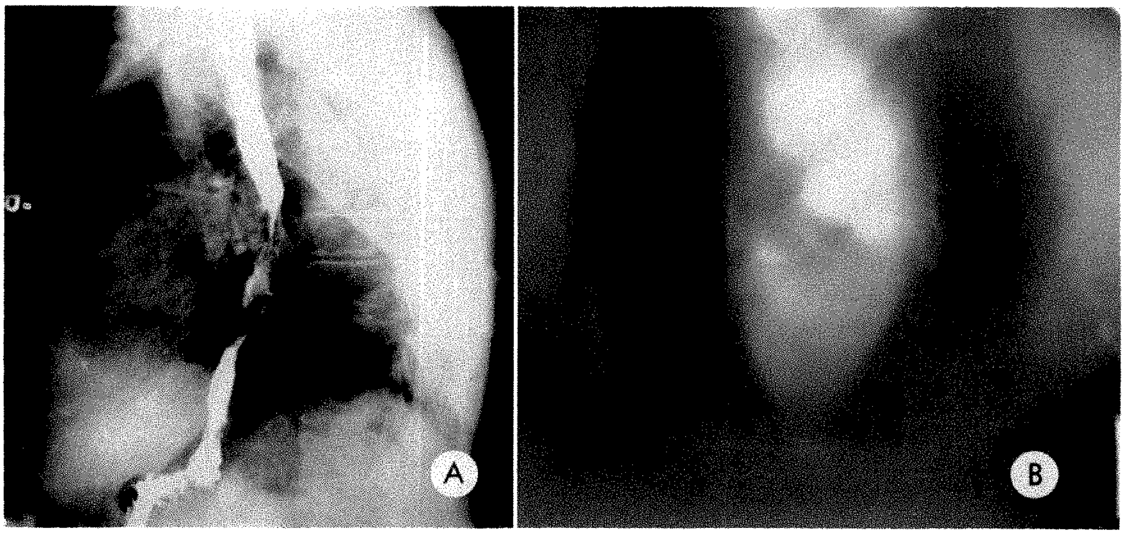
HORIZONTAL laminagraphy as a variation of body section roentgenography provides an anatomic cross section of a patient in a horizontal plane at any desired level.

Although the roentgenologic diagnosis of chest lesions is usually made on the basis of conventional posteroanterior and lateral roentgenograms, this method falls short in the evaluation of the mediastinum. The posteroanterior roentgenogram presents a superimposed view of the thoracic spine, vascular structures and sternum with the embedded trachea. Bulging of the margin



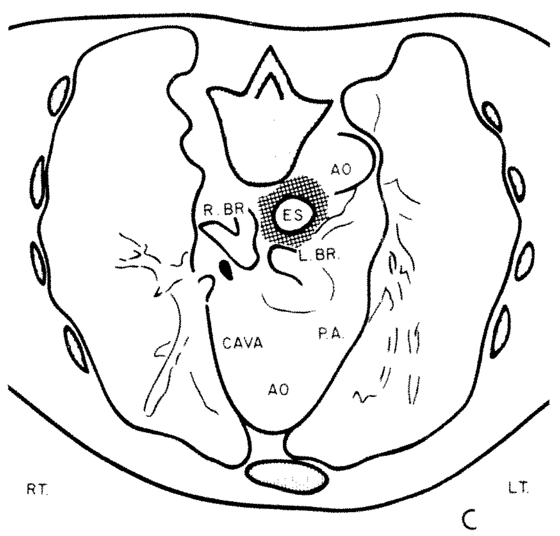


FIG. 1. Case 1. A seventy-five year old white male was referred to the institute with the diagnosis of carcinoma of the esophagus in the mid-portion (*A*). Azygography showed a complete outlining of the azygos system with some minor indentation in the upper one third, not very conclusive for extrinsic pressure, but important enough to warrant further investigation.

Horizontal laminagram (*B* and *C*), just below the bifurcation, does not show any signs of mediastinal lymph node involvement.

At surgery, the tumor was completely resected, and no mediastinal lymph node involvement was found.

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and alteration of the position and caliber of the trachea are the only easily recognizable features. Additional information is gained with oblique views, Bucky studies, vertical laminagraphy, fluoroscopic examination of the opacified esophagus and thoracic angiography. A further method to examine the posterior mediastinum is the azygos demonstration by intra-osseous injection,[9,17,21,29,31,34] which was performed in some of our cases.

Horizontal laminagrams disclose the spatial relationship and topography of the mediastinal organs, lungs and pleura better

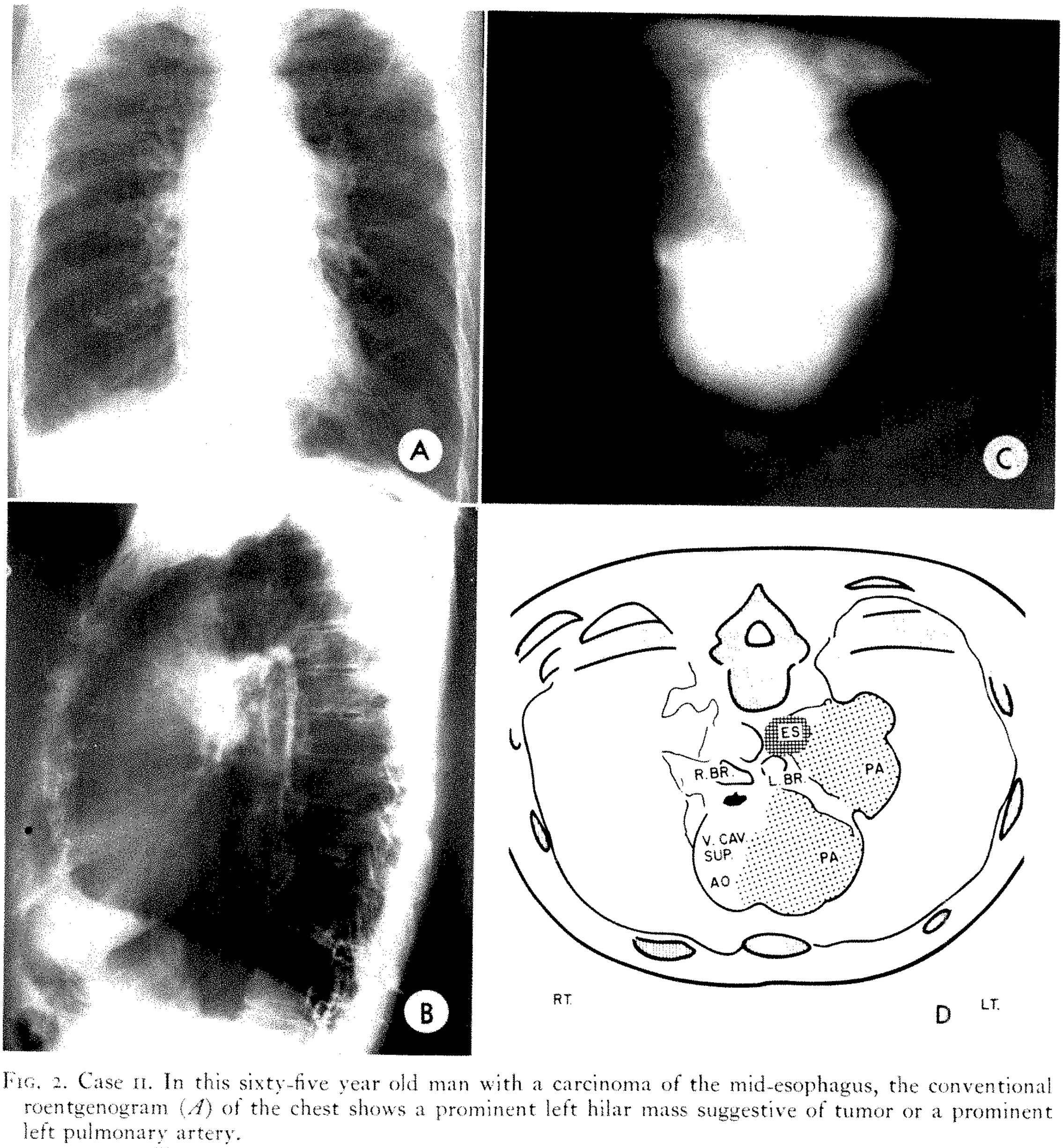
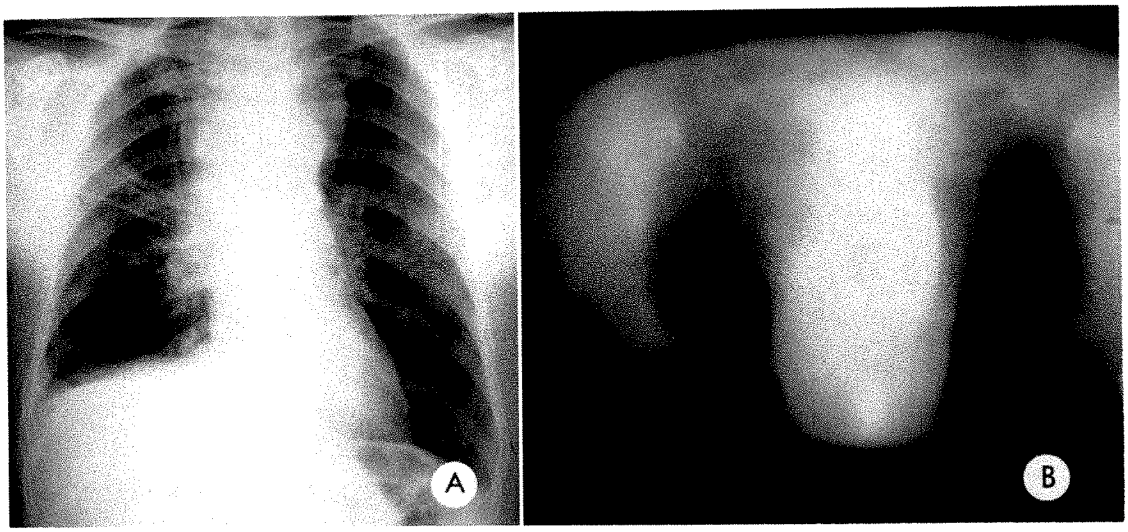


Fig. 2. Case II. In this sixty-five year old man with a carcinoma of the mid-esophagus, the conventional roentgenogram (*A*) of the chest shows a prominent left hilar mass suggestive of tumor or a prominent left pulmonary artery.

(*C* and *D*) Horizontal laminagram at the level just below the carina shows the pulmonary artery and particularly its left branch to be markedly enlarged. No hilar or mediastinal lymphadenopathy is seen. (*B*) Azygography demonstrates a patent azygos and hemiazygos system.

At surgery the tumor was found confined to the esophagus. Pulmonary stenosis and post-stenotic dilatation of the left pulmonary artery were evident.



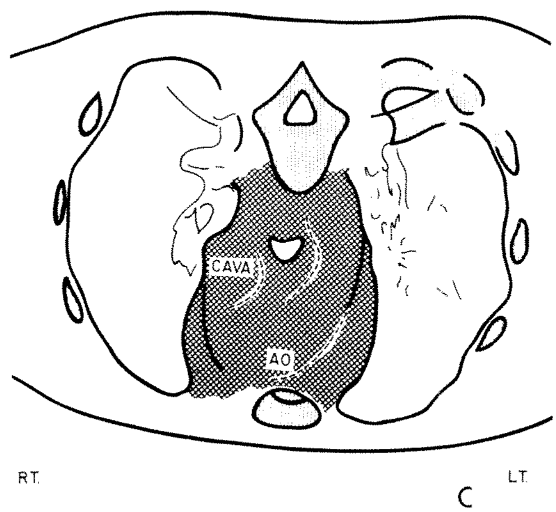


Fig. 3. Case III. A fifty-seven year old white male was referred to the hospital with the diagnosis of an oat cell carcinoma of the right upper lobe of the lung with extensive bilateral mediastinal involvement (*A*).
(*B* and *C*) With horizontal laminagraphy the spatial distribution of the huge mediastinal mass extending to the inlet is well outlined. In addition, old tuberculous changes in the posterior segment of the right upper lobe are seen.

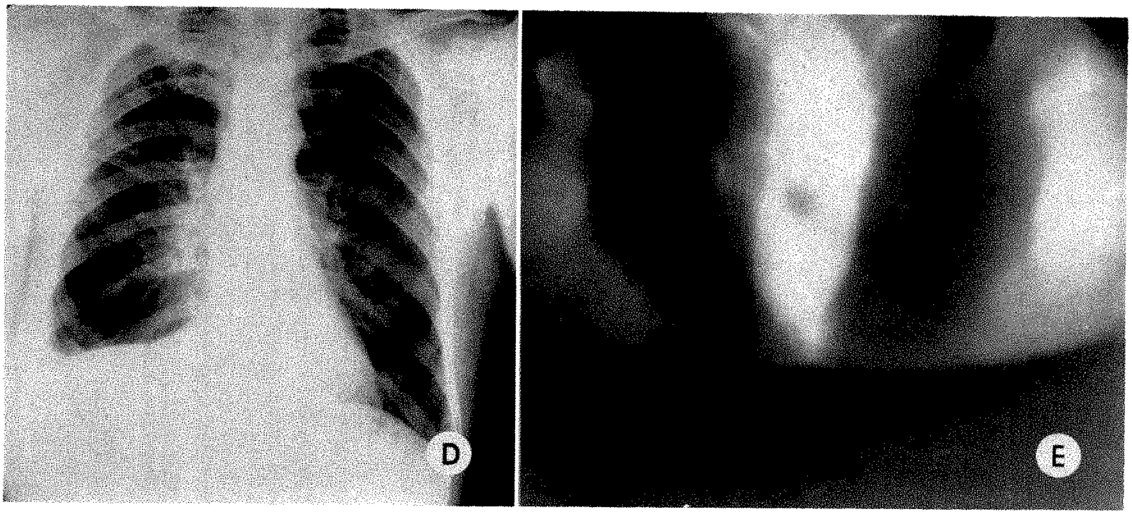
than the above mentioned methods and demonstrate more adequately otherwise obscured areas.[3]

Stimulated by Kieffer[14] of Norwich, Connecticut, the first workable laminagraph was built by Watson,[38] who was also the first to publish his findings. European investigators such as Vallebona and coworkers,[35,36] Amisano and his colleagues,[1,2] Gebauer and Schanen,[12] and others[15,16,20] promoted this method and an extensive bibliography has accumulated since, particularly in the Italian literature.[4,6,7,28]

Roswit *et al.*[25,26] and Wilk[39] in the United States contributed from their experience with this technique, and are impressed by its merits as a valuable tool in diagnosis and in treatment planning. In their papers and in that of Stevenson,[30] the efficiency of this method is described and an explanation of its physical principles is outlined.

For horizontal laminagraphy, a special laminagraphic unit is required, consisting of a chair and a cassette holder which rotate simultaneously in the same direction at the same speed during the exposure. A number of suitable units of different European makes are available. We used a laminagraph of our own construction which was built on the principles of commercially known units.

The exposure of the roentgenographic film is made in an angle of incidence of 23° at a focus-film distance of $7\frac{1}{2}$ feet, during a



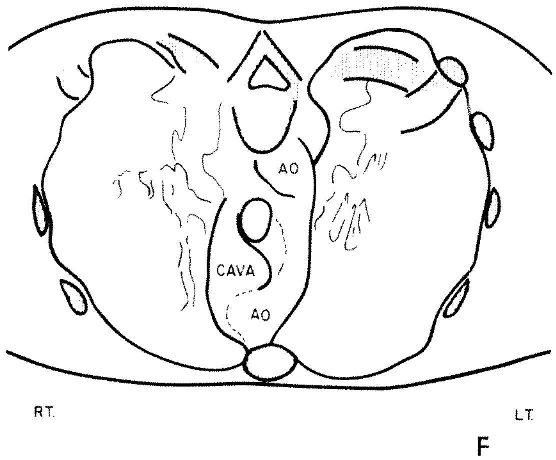
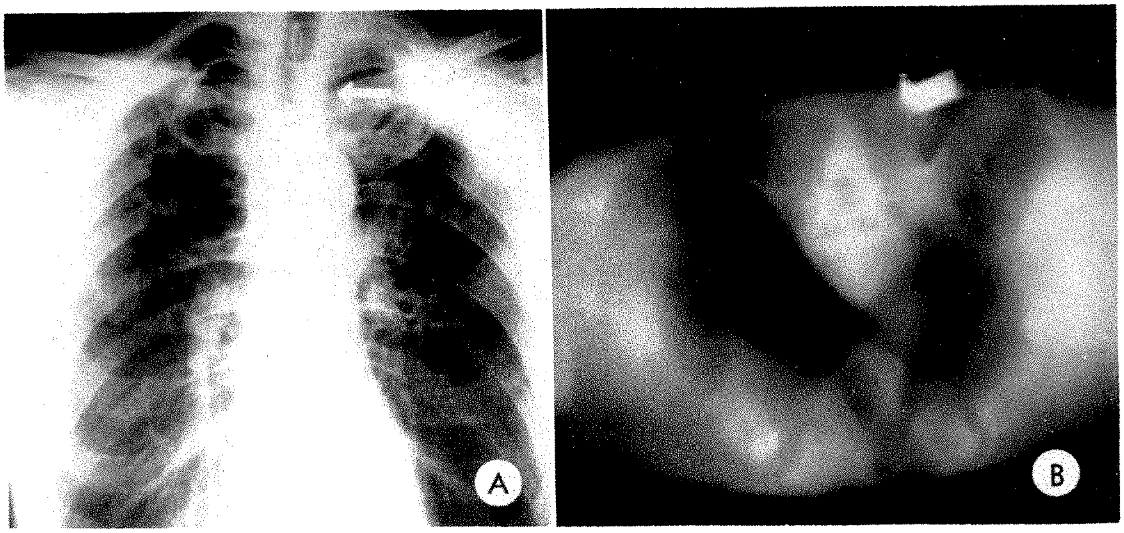


Fig. 3. Case III. (*D–F*) The control examination after radiation therapy shows complete regression of the mediastinal mass. This was confirmed at autopsy three months later.

complete revolution of patient and cassette. The thickness of the represented section is, according to Vieten,[37] about 0.3 cm. and depends on the angle of the incident beam. The technical factors used are: 65–80 kvp., 100 ma., 3 second exposure, high speed screens. The radiation dosage the patient is exposed to is 0.4 r (air) and has been considerably reduced with films and screens of increased sensitivity.[39,40] Proper alignment of the unit and narrow collimation of the beam[13] determine the quality of the laminagram. Exposures with a partial rotation as advocated by Lindblom[18] increase detail at the expense of increased blur from adjacent structures.

Horizontal laminagrams obtained in this fashion correspond with the descriptive cross section as used in an anatomic atlas.[10] They are free from distortion, and the blur effect commonly seen in conventional laminagrams is considerably less pronounced. Particularly dense structures in the vicinity of the represented section, however, can produce blur shadows and obscure the fine details which are known as "induced deformations."[12,24,33] Due to the tube-object-film distances, horizontal laminagrams show an enlarged image. The magnifying factor is constant for the set-up used, so that the actual size of any given structure can be measured with proportional calipers. Where life-size laminagrams are required, as for outlining and computing purposes in radiation therapy[11,12,22,25,32,35] or for the measurement of the volume of organs,[5,8] reduction to normal size is possible. Different devices have been described for this



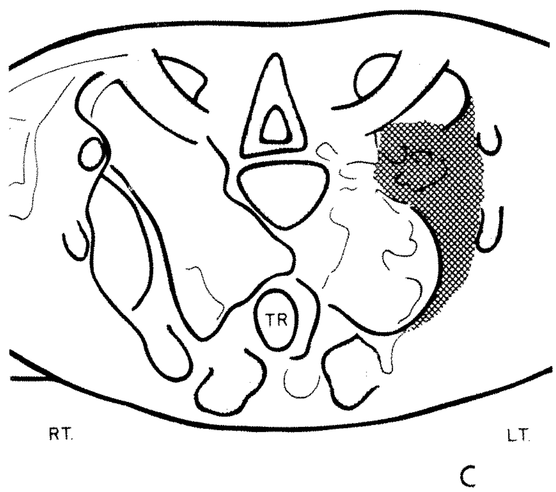


Fig. 4. Case iv. This is the case of a fifty-seven year old man with the clinical diagnosis of a left superior sulcus tumor (*A*) confirmed by biopsy.

(*B* and *C*) Horizontal laminagram at the level of D3-sternal notch shows a dense tumor mass about 8 cm. in extension attached to the lateral thoracic wall. There are no definite signs of mediastinal involvement. Incidental findings are fibrotic changes in the right upper lobe with slight retraction of the trachea towards the right. Sections through the tumor bearing area serve for therapy planning.

purpose.[23,26,39] We used a simple camera lucida which admits standard 14×17 inch roentgenographic films.

The level at which laminagrams were taken is readily identified by the structures reproduced on the film (bifurcation, sternoclavicular joints, etc.). Wilk[39] uses metallic rods of different lengths embedded in plastic material and fastened to the patient's chest wall. Other methods using similar devices are described.[11,26,41] All of them help to determine the section level and to repeat identical follow-up roentgenograms.

The present paper is published to report about our experience with horizontal laminagraphy. The objective of this investigation was: (1) to determine the usefulness of this method in tumors involving the lung, esophagus and mediastinum and (2) to study tumor extension and its differentiation from concurrent pathology. Our results are based on the evaluation of 68 cases of which all but 2 were proved histologically. The results from horizontal laminagraphy and conventional examination were correlated with the clinicopathologic findings. The patients submitted to this study were selected from a large number of cases treated in this institute. They represented either diagnostic problems or were referred for cross section roentgenography through the tumor bearing area for radiation treatment planning and dosage calculation.

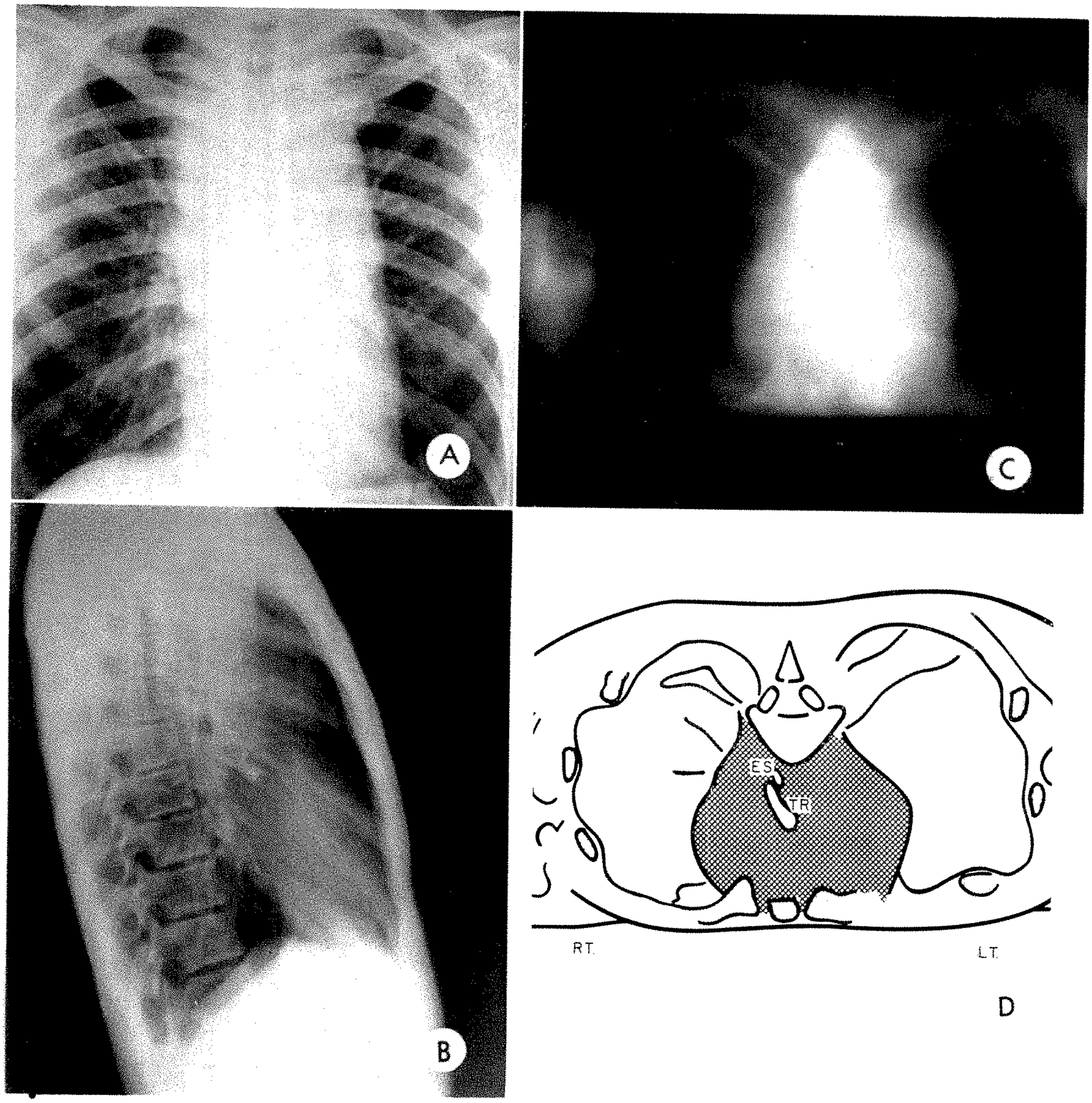


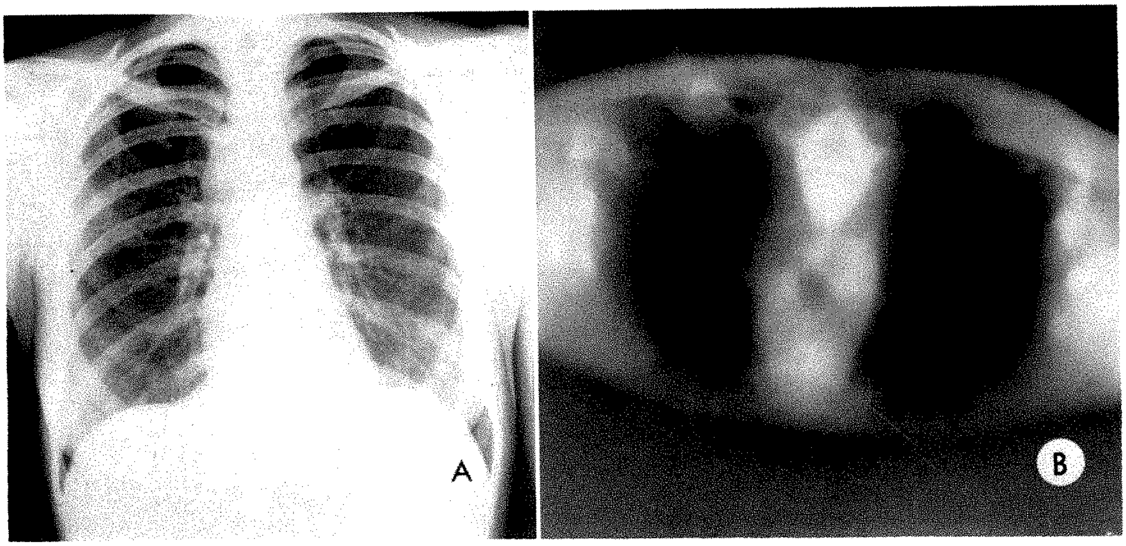
Fig. 5. Case v. This was a twenty year old white male with the diagnosis of mediastinal Hodgkin's disease. Posteroanterior and lateral chest roentgenograms (*A* and *B*) show huge bilateral mediastinal polycyclic masses.

(*C* and *D*) Horizontal laminagram reveals good outlining of the mass in the 3 compartments of the mediastinum with encroachment of the trachea.

DISCUSSION

The great number of different methods developed for the differential diagnosis of lesions of the chest and mediastinum show clearly the difficulty of this problem. Several investigators[2,12,36,39] have shown the usefulness of horizontal laminagraphy as a complement to other roentgenographic procedures.

In 27 cases of bronchogenic carcinoma, we have found that the tumor mass could be promptly differentiated from surrounding atelectases and effusions by virtue of their different density. A shift of the mediastinum as well as hilar involvement was also well seen. In 11 cases, distortion of the trachea due to extrinsic pressure and narrowing of its lumen was observed more



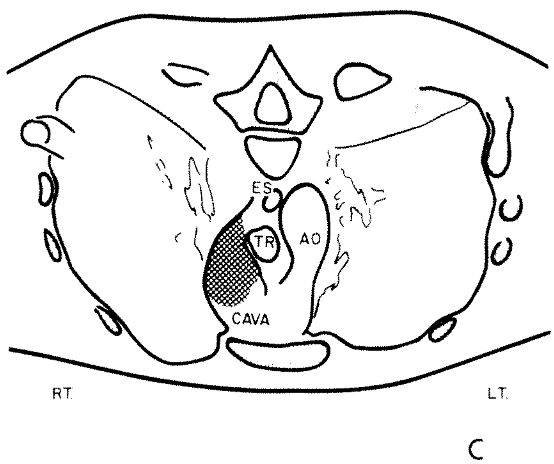


FIG. 6. Case VI. A forty-four year old housewife with the diagnosis of Hodgkin's disease had been treated with radiation therapy to various regions, including the mediastinum, four years ago. At the time of this examination, the patient was asymptomatic. However, the conventional posteroanterior roentgenogram (*A*) shows a well-defined, convex mass at the level of the right main bronchus extending in a vertical direction.

(*B* and *C*) Horizontal laminagram shows this mass with well-defined borders lying to the right of the esophagus, anterior to the thoracic spine and extending towards the vena cava superior. The diagnosis of a prominent azygos vein was made, most likely due to postirradiation fibrosis. This was confirmed by azygography.

distinctly than by vertical laminagraphy. Three patients had the additional finding of cavity formation which in one case showed extension to the lateral pleural space not seen by vertical laminagraphy.

In carcinomas of the esophagus, the choice of treatment is determined by the topographic relation of the tumor and the presence of lymph node involvement. Although the diagnosis is based on the conventional barium swallow and esophagoscopy, horizontal laminagraphy has shown to be an aid in analyzing the size of the tumor and its relation to adjacent structures. Twenty-one cases with esophageal tumors were examined. In 12 cases, the lesion was confined to the upper third and in 8 of these a displacement and encroachment of the trachea were visible. Of course, in all the lesions, the exact extension of the tumor mass could be demonstrated. In 6 cases of lesion of the mid-third of the esophagus, the determination of expansion in regard to the related structures, as pulmonary vessels, and the main bronchial system was found to be most valuable and of benefit for the treatment planning. It is our impression that in these lesions, horizontal laminagraphy is superior to all conventional methods. In the 3 cases with lesions of the lower third of the esophagus, the extent of the tumor was well demonstrated, but no additional information was obtained. Due to the absence of any dense

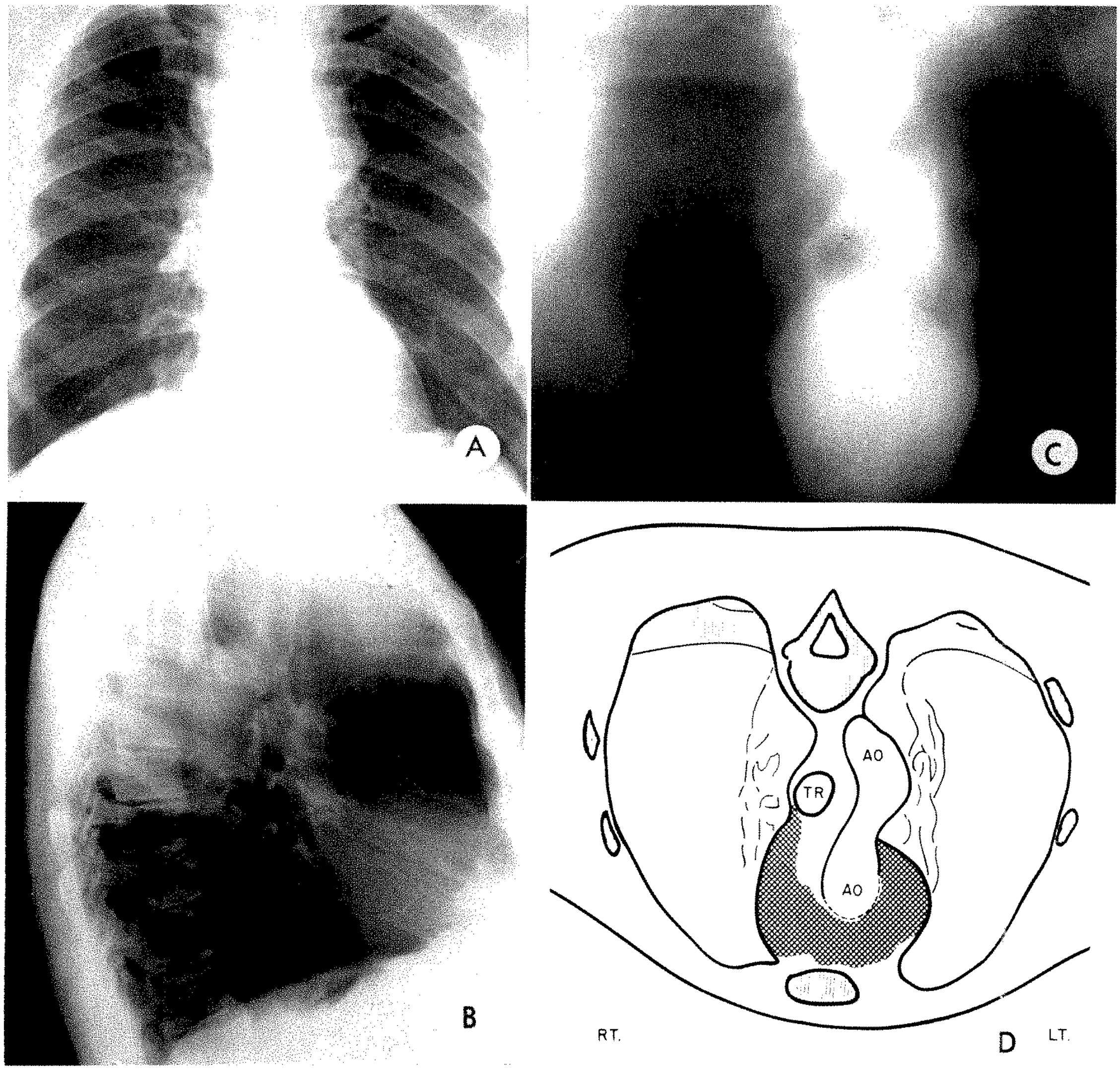


Fig. 7. Case vii. This white male, sixty-nine years of age, was admitted to the hospital for evaluation and treatment of an anterior mediastinal mass. The anterior and upper borders of the tumor appear well defined and symmetric on the conventional roentgenograms (*A* and *B*). Yet the extent of the mass in its posterior direction and its relation to the great vessels cannot be demonstrated with these procedures. (*C* and *D*) Horizontal laminagram shows a well-delineated mass in the anterior mediastinum measuring about 9 cm. across, encompassing the ascending aorta, the superior vena cava and extending towards the trachea. No signs of hilar lymphadenopathy are present.

At surgery a benign encapsulated thymoma was found.

organic structures in the retrocardiac space, a tumor can be easily visualized in this area. An attempt was also made to study the barium-filled esophagus during the examination but was not very successful due to the considerable blurring of the heavy contrast medium. Stevenson[30] has used a nasogastric tube filled with opaque material which gave him a satisfactory orientation on the roentgenograms. Other authors[19,22] report in the Italian and French literature the usefulness of a pneumomediastinum during the examination which enables them to outline the outer esophageal wall.

In the majority of mediastinal tumors,

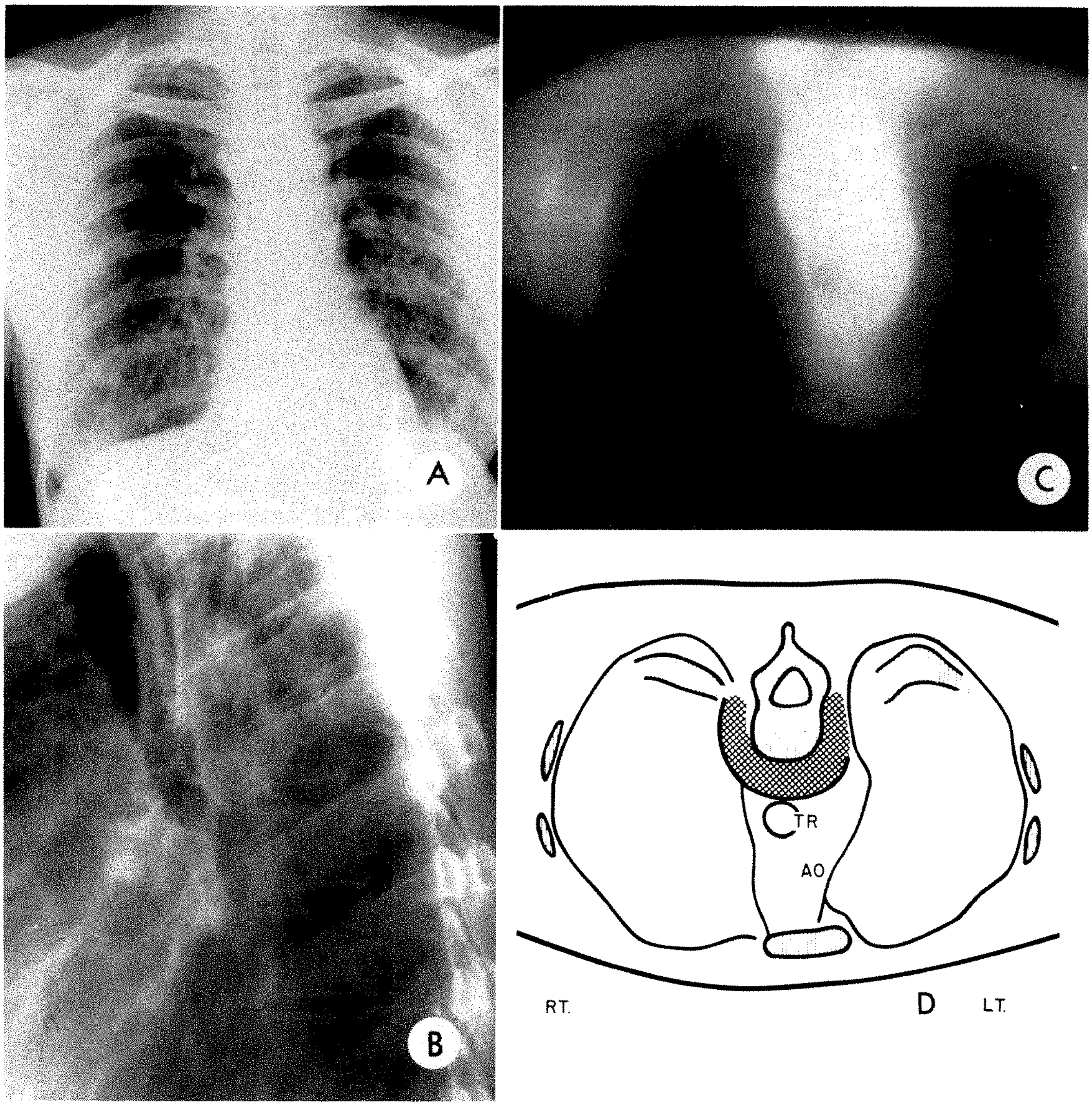


FIG. 8. Case VIII. This forty-three year old white housewife was referred to this institute with the diagnosis of Hodgkin's disease.

(*A* and *B*) Posteroanterior and lateral roentgenograms reveal numerous nodular infiltrations in both lungs and a slight bilateral mediastinal widening at the infraclavicular level. On the lateral roentgenogram, a wedge shaped compression of D4 is noted.

(*C* and *D*) Horizontal laminagram taken at the level of the fourth dorsal vertebra reveals a well-delineated localized soft tissue mass engulfing this vertebral body in a U-like fashion, indicating the presence of a soft tissue mass. The mid- and anterior mediastinal compartments are normal.

identification is readily made by conventional roentgenographic procedures and horizontal laminagraphy does not offer significant additional information. However, in isolated cases with a differential diagnostic problem, a more comprehensive view of the three mediastinal compartments can be obtained. In the 20 cases studied with this method, important diagnostic details could be attained.

The appreciation of the appearance of the tumor, its boundaries, localization and sometimes its symmetry furnished diagnostic clues in spine involvement and in

thymomas. A prominent azygos vein could be differentiated from tumor recurrence. Because of the difference in densities between solid tumor masses and areas of fibrosis and atelectasis, recurrent disease could be ruled out. Displacement and encroachment of the trachea were more accurately outlined, especially by the observation of changes in the size and the shape of the tracheal lumen. Another advantage of this method lies in the clinical and therapeutic follow-up of patients where control examinations carried out after chemotherapy or irradiation serve as an objective record in evaluating the change in size of a tumor mass.

SUMMARY

Horizontal laminagraphy as a supplemental diagnostic method was employed to determine its usefulness in the evaluation of tumors of the lung, esophagus and mediastinum. Sixty-eight cases were studied, of which 27 were bronchogenic carcinoma; 21, esophageal carcinoma and 20, lymphomas. The findings are presented and correlated with the information gained by conventional roentgenographic procedures. Clear delineation of topographic-anatomic detail with this method permits detection of relatively minor deviations from normal. Not only are gross structures well outlined but the relationship of a tumor mass can be more adequately determined, making this procedure a valuable diagnostic aid in certain cases.

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X-RAY IMAGE INTENSIFICATION WITH A LARGE DIAMETER IMAGE INTENSIFIER TUBE*

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When x-rays penetrate an object, the local x-ray attenuation depends on both the thickness and atomic number of the elements forming the object under scrutiny. Thus, the intensity pattern in the x-ray beam after penetration of the test object contains information concerning the structure of the object.

This structural information is generally made visible by a fluorescent screen converting the x-rays into visible light. The intensity pattern of the x-ray beam can now be recognized as a brightness pattern on the fluorescent screen.

The x-ray doses used for medical application may not exceed certain limits, as otherwise physiologic and genetic damage results. This limitation, together with the relatively low intrinsic efficiency of x-ray sensitive phosphors, sets light levels on the fluorescent screen which are at best comparable to the illumination of a landscape by the full moon.

The observer of such a low brightness pattern is forced to utilize rod rather than cone vision, leading to decreased detail perceptibility. Thus, the observer is unable to perceive all information originally contained in the x-ray beam.

While the physiologic limitation of the human eye inhibits the full utilization of the intelligence contained in the x-ray beam, a further physical limitation is represented by the "quantum fluctuations."

As discussed in detail by Tol, Oosterkamp and Proper,[7] the perceptibility of contrast and detail is connected by the relations:

$$C = (B_2 - B_1)/B_1 = k/\sqrt{\overline{N}} \qquad (1)$$

wherein C = contrast; B_1, B_2 = brightness of two information elements; $\overline{N}$ = average number of radiation quanta incident on each information element per second; and k = constant.

X-ray quanta are emitted from the target in the x-ray tube in statistical distribution with time as the independent variable. The random nature of quantum emission becomes less visible to the human eye as the number of quanta per second, incident on the area of scrutiny, increases. The number of quanta may be increased by increasing the area of scrutiny (decreasing detail perceptibility) or by increasing the radiation intensity.

Equation 1 represents the fundamental limitation of contrast-detail perceptibility due to quantum fluctuations. It is not possible at present to circumvent this limitation by other means than storage, and with this approach the length of the storage time, necessarily longer than the accumulation time of the human eye, reduces the time resolution of the information obtained.

The average number of quanta $\overline{N}$ to be used in Equation 1 is the lowest number of quanta per second per unit area found anywhere in the image converting and intensifying system.

In a simple chain, consisting of x-ray emitter-object-fluorescent screen-observer, the "quantum sink" lies in the eye of the observer. In an image intensifying system, the quantum sink is located generally, but not always, in the element of first energy conversion (x-rays to visible light). Furthermore, the quantum sink is now not as deep as for image conversion without intensification. Thus, the contrast-detail perceptibility is increased at a given x-ray intensity.

Cinefluorography is widely used in modern roentgenology.[2] The application of

* From the Rauland Corporation, Chicago, Illinois.

cinematography to radiology leads to a substantial increase in x-ray doses with the disadvantages mentioned above. The available number of light quanta in cinefluorography utilizing standard fluoroscopic screens decreases with increasing frame rate, imposing a limitation on the application of cinefluorography. This disadvantage can be remedied by the use of image intensification.

The application of television techniques to roentgenology offers new possibilities in medicine. Television fluoroscopy of manageable complexity generally requires image intensification previous to the television pick-up device.

The advantages of image intensification in radiology may be summarized as follows: (a) increased contrast-detail perceptibility at maintained radiation level or (b) maintenance of contrast-detail perceptibility at reduced radiation level; (c) extension of the field of application of monoplane and biplane cinefluorography; and (d) reduction in the complexity of equipment in television fluoroscopy.

SURVEY OF X-RAY IMAGE INTENSIFYING SYSTEMS*

The proposed or existing x-ray image intensifying systems may be divided into three groups: (1) electronic systems; (2) solid state systems; and (3) vacuum tube systems.

The principles of these three types of x-ray image intensifying systems are summarized below.†

1. ELECTRONIC SYSTEMS

The electronic intensifying systems convert the information contained in the x-ray beam directly, or by means of an intermediate energy conversion, into an electrical signal. The signal thus obtained is fed into a video amplifier and displayed on a television picture tube. Electronic intensifying systems cannot deliver any other form of presentation but a televised image.

Two systems in this group are to be mentioned: (a) image Orthicon pick-up from a standard fluorescent screen; and (b) direct pick-up with an x-ray sensitive Vidicon.

The image Orthicon pick-up is accompanied by the inherent electronic complexity of the system, while the photoconductor used in the x-ray sensitive Vidicon possesses decay properties which require at present the use of high energy, pulsed x-rays at low average intensity levels. Besides the inconvenience of using a rather complex pulsed x-ray system, the increased x-ray scattering due to the use of high energy x-rays together with the increased quantum noise due to low intensity operation decreases the contrast detail reproducibility of this device, a result which is particularly undesirable for medical application.

2. SOLID STATE SYSTEMS

Two devices ought to be mentioned here: (a) opto-electronic mosaic ("image converting panel"); and (b) field enhanced photoluminescence.

Each information point of the opto-electronic mosaic consists of a photoconductor and an electroluminescent element in series. When the impedance of the photoconductor is changed by impinging light or x-rays, the potential drop across the electroluminescent element increases, leading to light emission. The low speed of response and the structure of the panel seem to present difficulties in the practical application of such devices.

Field enhanced, x-ray induced photoluminescence is shown by certain phosphors, such as CdS:Mn. These materials display an enhancement of x-ray induced fluorescence when an AC-field is applied simultaneously with the x-ray excitation. As no exact brightness values relative to the brightness of a standard fluorescent screen, such as Patterson CB-2, are available, the merits of this method cannot be discussed here.

* Linden[4] has also given a summarized description of x-ray image intensifying systems.

† These three systems postulate an x-ray beam flooding the area of scrutiny.

3. VACUUM TUBE SYSTEMS

The systems forming this group may be classified as follows: (a) direct conversion from x-rays to electrons *in vacuo;* (b) conversion from x-rays to visible light taking place *outside* of the vacuum image intensifier; and (c) conversion from x-rays to visible light taking place *inside* the vacuum intensifier.

A direct conversion from x-rays to electrons has been described by Huang[3] and applied to a novel x-ray microscope. The system uses as its x-ray receiving surface a metal foil. The impinging x-ray quanta release Compton-electrons which are multiplied by a back surface secondary electron emitting layer. This composite surface is inserted in an immersion objective of an electrostatic electron microscope. As the Compton-electron yield is rather low, this system is presently limited with respect to both the brightness gain and the contrast-detail reproducibility which may be obtained.

Another system utilizes *conversion from x-rays to visible light outside the vacuum tube.* The x-ray quanta are converted into light quanta by a standard fluorescent screen. This primary x-ray image is minified and projected by a highly efficient Schmidt optical system onto the semitransparent photocathode of a vacuum tube image intensifier with unity magnification. The "quantum sink" may be shifted, in this system, from the fluorescent screen to the coupling light optical system and is then deeper, thus limiting the system as to both resolution and contrast reproduction.

Systems utilizing *conversion from x-ray to visible light inside a vacuum tube intensifier* are commonly known as "x-ray image intensifiers."[1] X-rays penetrate through a window into the vacuum space of the tube and are converted into light quanta by a fluorescent screen. A semitransparent photocathode, in physical contact with the phosphor screen, converts the light quanta into photoelectrons without loss in resolution. An electron optical system accelerates and focuses the electrons onto the viewing screen where they are reconverted into light quanta. The brightness distribution on the viewing screen represents an exact replica of the intensity distribution in the x-ray beam.

X-ray image intensifying tubes of this type seem to yield presently the highest light gain combined with the best contrast-detail reproducibility. However, tubes of this type have had a rather small pickup screen diameter (five inches or less) until recently.

LARGE DIAMETER IMAGE INTENSIFIER TUBE

The development of x-ray image intensifiers with a large pickup screen diameter and high light gain and resolution presented formidable obstacles of a technologic nature. As tubes complying with the requirements of large pickup, high brightness gain, high resolution, and good contrast-detail reproducibility can be used universally in radiology (specific application, cardiology), cinefluoroscopy, radioscopy and television fluoroscopy, as well as in industrial roentgenology, an effort will be undertaken to describe in detail both the design and operation of such a tube having a useful pickup screen diameter of $8\frac{1}{2}$ inches.

GENERAL DESCRIPTION

The x-ray image intensifier discussed here consists of a hard glass envelope, the two halves of which are joined together by heliarc Kovar flanges (Fig. 1 and 2). A relatively thin-walled spherical dome forms the x-ray window and houses the composite pickup screen on a separate support $8\frac{1}{2}$ inches in diameter.* The dome also carries the cathode contacts.

The cylindrical portion of the envelope is covered on the inside with a conductive coating which serves as a focus electrode and is electrically connected to the Kovar flange. The shoulder region of the tube envelope carries on the inside a semicon-

* The merit of directly depositing the composite pickup screen onto the spherical x-ray window will be discussed later.

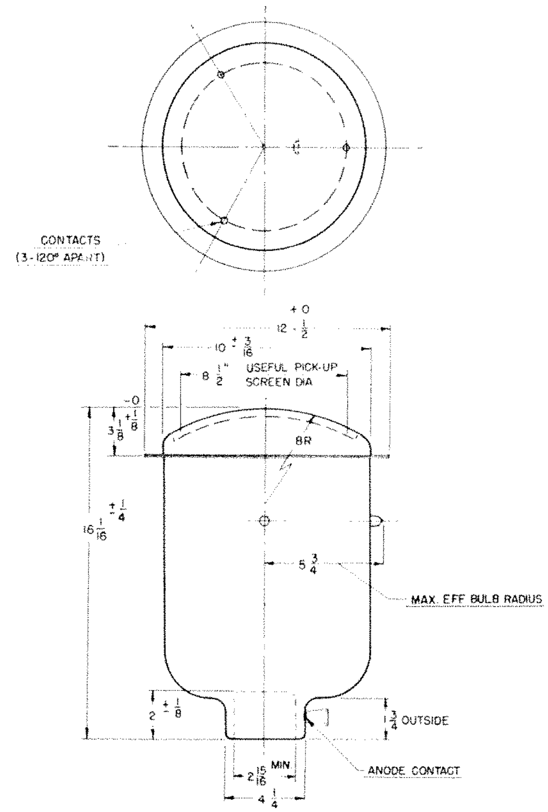

Fig. 1. Dimensional view of the large diameter x-ray image intensifier tube.

ductive coating called "high voltage coating."

The re-entrant seal contains a bullet-shaped metal anode enclosing the aluminized viewing screen. The high voltage contact is located in this region.

The outside glass diameter of the envelope is 10 inches, the over-all length of the tube is 16 1/16 inches. The re-entrant seal has an inside diameter of 2 15/16 inches and a depth of 2 1/8 inches; thus, the viewing screen is easily accessible to a light optical system. The weight of the tube is approximately 7 pounds. The geometric dimensions and the weight indicate that the image intensifier tube can be incorporated conveniently in standard x-ray installations.

The light gain of an x-ray image intensifier is defined as the ratio of the brightness on the viewing screen of the device to the brightness of a standard fluorescent screen, both excited by identical x-rays. The brightness gain of the intensifier is due to both the geometric minification employed and an actual flux gain. A minimum brightness gain of 1000 is obtained with the tube described here.

Fig. 2. Photograph of the x-ray image intensifier tube.

After this general description, the tube components and some of the techniques applied in producing this device will be discussed in detail. Finally, examples of the performance of this device will be given.

Glass Envelope

As mentioned above, the glass envelope consists of two halves: the x-ray transparent dome and the anode half. The spherical dome is made of hard glass with a relatively high x-ray transparency, while the anode half consists of hard glass with appreciable x-ray attenuation, thus reducing the thickness of the required outside lead shielding. The viewing window in the re-entrant seal consists of optically clear glass.

Design of the Glass Dome and Location of the Pickup Screen. The tube is designed in such a manner that the pickup screen support touches the glass dome from the inside along its entire perimeter. The influence of this design on the viewable size of an object outside the tube can be appreciated if one considers a flat phantom or object to be x-rayed, positioned in such a

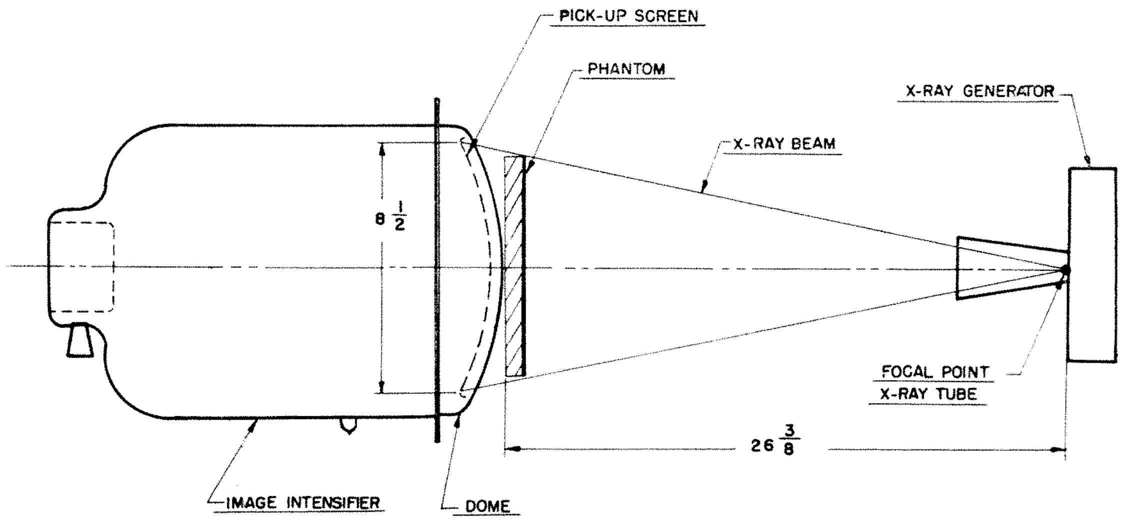

Fig. 3. Dimensional line drawing of an x-ray installation, using an x-ray image intensifier tube.

way that it touches the glass dome of certain curvature from the outside (Fig. 3). It can be seen immediately that the geometric magnification to which the shadow image of the phantom is subjected depends only on the axial spacing between the edge of the pickup screen and the center of the glass dome. This spacing, in turn, is fixed by the radius of curvature of the dome if the perimeter of the pickup screen touches the inside of the glass dome.

Applying the pickup screen directly to the glass dome of maintained curvature does not influence the viewable phantom size if an independent pickup screen support touches the glass dome as described above, as the geometric magnification is again determined by the curvature of the dome. Generally, the radius of curvature of the pickup screen is preferably made larger than the radius of curvature of the dome, for electron-optical reasons to be given later. Making the dome also of the smaller curvature would reduce somewhat the geometric magnification; however, the increase in glass thickness, required to maintain implosion safety, would increase the x-ray attenuation in the dome appreciably and thus result in a reduction of brightness gain. Furthermore, severe linearity distortions may result.

We may assume that the phantom to be observed through the image intensifier is two-dimensionally flat. As the pickup screen is always curved, the projection of the flat phantom onto the spherical pickup screen will lead to pincushion and linearity distortions. For a given x-ray beam divergence, these distortions depend solely on the curvature of the pickup screen.

A linearity distortion can be expressed by:

$$d_2'/d_1' \gtrless d_2/d_1 \qquad (2)$$

where

d_1, d_2 = radial spacing from the center of the flat phantom,

d_1', d_2' = the same spacings projected onto the pickup screen.

If d_1 and d_2 are projected by a divergent x-ray beam onto a flat receiving surface (Fig. 4), we can write

$$\left.\begin{aligned} d_1' &= d_1(a+x)/a \\ d_2' &= d_2(a+x)/a \\ d_2'/d_1' &= d_2/d_1 \end{aligned}\right\} \qquad (3)$$

If the projection occurs onto a spherical surface (Fig. 4), x in the above equation has to be substituted by x_1 and x_2 with $x_2 > x_1$ for a convex surface, thus indicating a linearity distortion. It follows now:

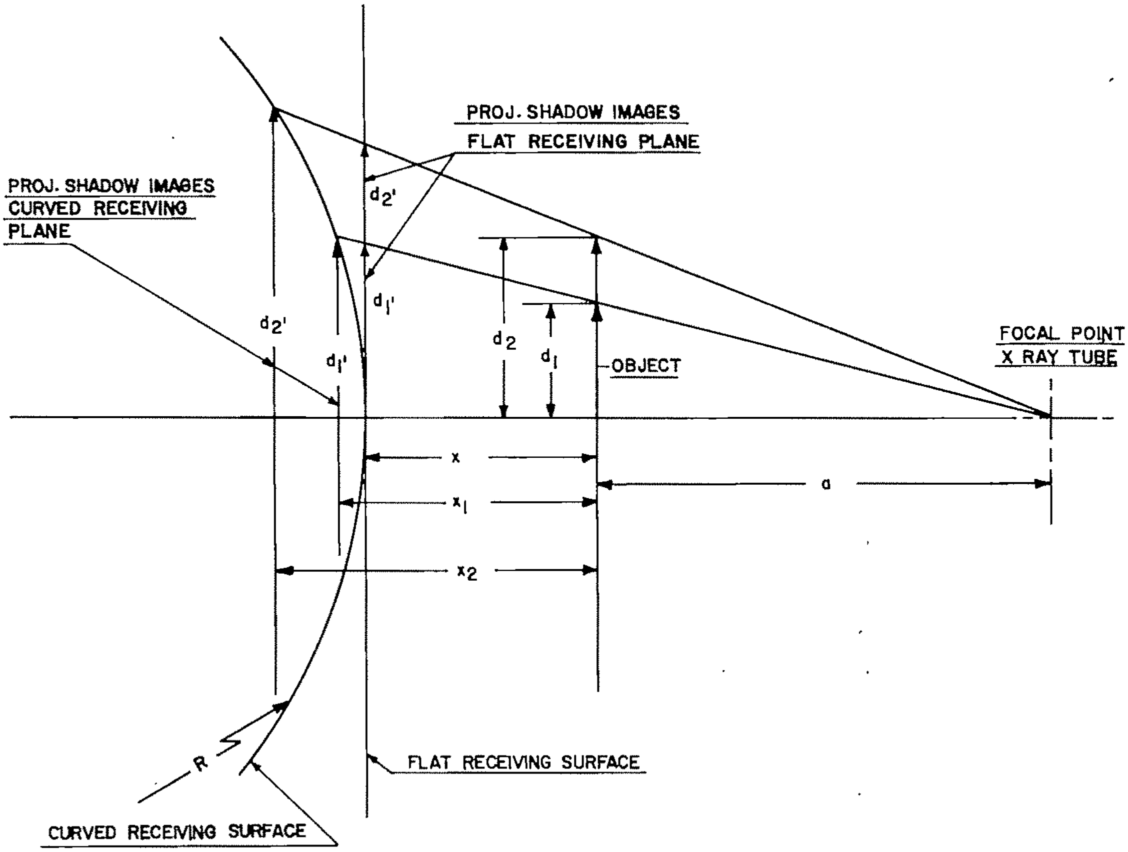

FIG. 4. Projection of a flat phantom onto a flat and curved receiving surface.

$$\left.\begin{array}{l} d_2'/d_1' = (d_2/d_1)[(a + x_2)/(a + x_1)] \\ (a + x_1)/(a + x_2) < 1 \\ d_2'/d_1' > d_2/d_1 \end{array}\right\} \quad (4)$$

An expression for x_i may be obtained from Figure 4, using elementary geometry:

$$x_1 = x + R - \sqrt{R^2 - d_1'^2} \quad (5)$$

Equation 5 indicates the increase of linearity distortions with increasing curvatures showing that a flat cathode leads to the least distortion, as expected. Thus, without loss in viewable phantom size, the utilization of a separate screen support minimizes linearity distortions at maintained x-ray transmission of the window.

A spherical window of constant thickness penetrated by a divergent x-ray beam shows increasing x-ray attenuation with increasing radial distance from the center of the window, as marginal rays in the x-ray beam do not penetrate the window perpendicularly, but under an ever increasing angle.

We see in Figure 5 that the effective thickness of the dome as a function of the geometric dimensions of the system considered here is described by:

$$d_r = d/\cos\left\{\text{arc } tg\left[\frac{r}{\ell + R(1 - \sqrt{1 - (r/R)^2})}\right] + \text{arc}\sin(r/R)\right\} \quad (6)$$

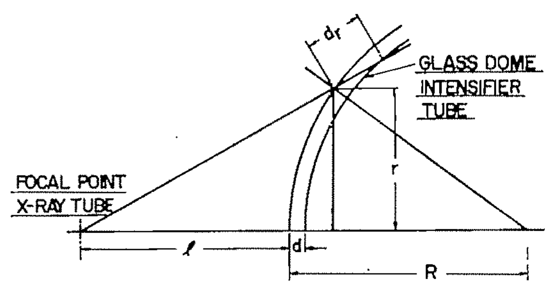

FIG. 5. Geometry used for the derivation of equation 6.

Table I

$R=8''$ $d=0.080''$ $l=24''$ $r_{MAX}=5''$

r (inch)	d_r (inch)
0	0.080
1	0.081
2	0.087
3	0.092
4	0.103

The meaning of the symbols used can be seen in Figure 5. A numeric example is given in Table 1.

The resulting transmission change depends on the first derivative of the exponential transmission equation for the thickness values under consideration and thus on the mass absorption coefficient of the window material.

The radially increasing attenuation may be compensated by decreasing the window thickness as the radial spacing from the center increases. The thickness of the window as a function of the radial spacing is expressed as follows (with $d \equiv d_{r=0}$):

$$d_r = d \cos \left\{ \text{arc } tg \left[\frac{r}{e + R(1 - \sqrt{1 - (r/R)^2})} \right] + \text{arc cos } \sqrt{1 - (r/R)^2} \right\} \sqrt{1 - (r/R)^2} \quad (7)$$

The radial transmission change of the glass dome is less than 2 per cent considering the glass thickness tolerances and the radial attenuation increase for a typical geometry of medical x-ray installations.

Anode Half. The anode half, consisting of rather low x-ray transparent hard glass, carries the viewing window in a large diameter re-entrant seal. The viewing window is made of optically clear hard glass to permit a faultless pickup of the reproduced image by a light optical system. As mentioned before, the diameter of the re-entrant seal is sufficiently large to make possible the insertion of the lens element of the optical system.

PICKUP SCREEN

Geometric Considerations. The composite pickup screen is supported by a spherical aluminum disk. The x-ray attenuation of the support aluminum is negligible and it may be assumed that practically all x-rays penetrating the dome impinge onto the x-ray sensitive phosphor layer, where they are converted into "blue" light quanta.

If the phosphor coating is irradiated by a divergent x-ray beam, the effective thickness of a uniform coating is greater in the peripheral area than in the center area. This effect leads to a slight brightness increase, as the energy conversion of an x-ray phosphor screen increases with increasing thickness till saturation is obtained. However, inherent "blurring" (x-ray scattering) increases also with increasing thickness. On the other hand, the peripheral resolution is generally somewhat lower than the central resolution (due to the image plane curvature, to be discussed later), if a uniform thickness coating is employed. It has been found that adequate compensation may be achieved by making the center thickness somewhat greater than the peripheral thickness. This correction determines the curvature of the pickup screen surface and lies in the order of several mils.

The curvature of the pickup screen surface is an important electron optical parameter. The curvature $1/R_S$ of the surface can be determined from the curvature of the support $1/R$, the diameter of the support disk $2r$, and the thickness difference Δt, by the following relation, given here without proof:

$$R_S = 0.5 \left[\frac{r^2}{(R - \Delta t) - \sqrt{R^2 - r^2}} + (R + \Delta t) - \sqrt{R^2 - r^2} \right] \quad (8)$$

If we assume $\Delta t \leq 0.005$ inches, it can be seen that $R_S \leq 1.01 R$ for a wide range of possible values of R. Thus, for electron optical purposes, it is permissible to utilize the value of R instead of R_S. Equation 8 shows also that small, localized variations of R_S do not appreciably influence the electron-optical properties of the system.

Selection of Phosphor and Coating Thickness. The applied phosphor emits essen-

tially in the blue band, as the SbCs photosurface used in the tube possesses the highest quantum efficiency for blue light. In addition, phosphors emitting in the blue band, under x-ray bombardment, yield a high quantum efficiency.

The particle size of the phosphor is such that the pickup screen resolution is limited by x-ray scattering rather than by the statistical distribution of the grain of the light emitting particles.

The persistence of the phosphor is medium.* The decay after DC x-ray exposure of longer than 10 seconds at intensity levels commonly used in fluoroscopy and cineroentgenography is fast enough to permit both the imaging of any moving process within the human body and mechanical scanning with the image intensifier tube during operation.

The thickness of the screen consisting of phosphor embedded in silicon resin has been selected in such a way that the response to x-rays is "linear," between 75 and at least 100 kv. peak accelerating potential of the x-ray tube (Fig. 6). An approximately 20 per cent lower gain results for operation between 200 and 250 kv. peak.

However, the saturation thickness has not been reached for any operational x-ray wavelength. In other words, some screen brightness has been sacrificed to minimize blurring.

Phosphor Surface and Barrier Layer. The semitransparent photosurface, applied directly on top of the phosphor-resin layer, requires the phosphor surface to be as smooth as possible, as a microscopically rough surface decreases the sensitivity and increases the resistance of the photo-emissive layer.

If electrons are emitted from a surface element dF of the photo-emissive layer, this surface element could assume a more positive potential than the surrounding area if connected to the cathode contact through a high resistance. This effect would alter the potential gradient in front of dF and would lead to values of gamma of the device smaller than one, if the potential gradient drops below a limiting value (space charge limited emission of the photosurface). In addition, the speed of the device might suffer as the charging time of dF increases considerably.

A transparent, very thin resin coating is cast over the resin-phosphor layer to achieve the required microscopic smoothness of the surface. The gloss of a surface prepared in this manner has been determined to be only 2–3 per cent lower than the gloss of a polished glass surface.

Elements of the first group of the periodic table, such as Cs and Na, act as negative catalysts for the silicon resin in the pickup screen at elevated temperatures.

The phosphor surface has, therefore, to

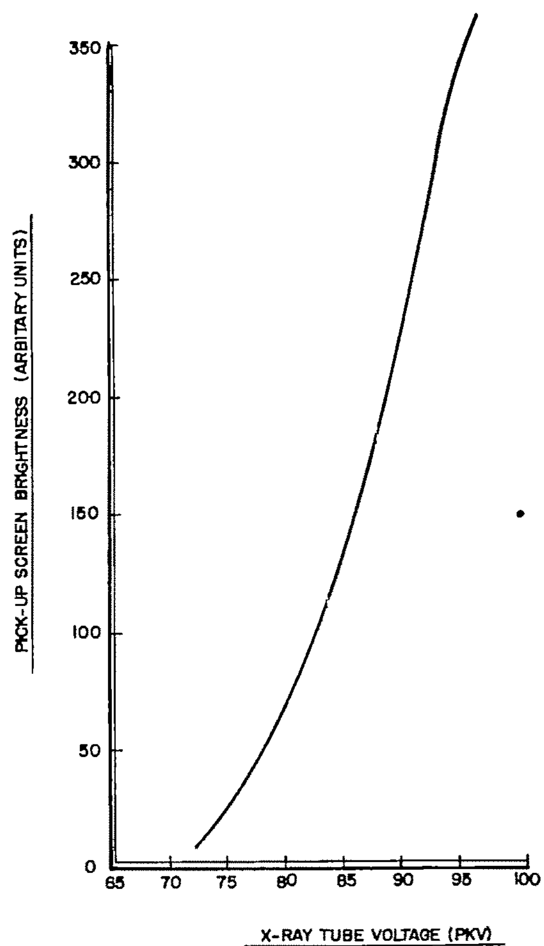

Fig. 6. Brightness of the pickup screen as function of the x-ray wavelength (accelerating voltage).

* Generally, the persistence of x-ray phosphors increases with increasing exposure time for short exposures.[8]

be sealed off by a transparent barrier layer in order to avoid the decomposition of the silicon resin in the presence of Cs at the temperature required for processing the photosurface.

Aluminum oxide is used as the barrier layer material. It is known that Al_2O_3 exists in two forms: the tightly packed and the porous versions. The porous version, which is not self-sealing against oxygen, is not sealing against Cs either. A tightly packed Al_2O_3 layer with excellent properties as a barrier layer against Cs may be readily obtained by heating a thin evaporated aluminum layer in dry air.

VIEWING SCREEN

The cathodoluminescent silver activated ZnS phosphor is settled on a substrate of optically clear glass. The phosphor used has an intrinsic energy efficiency of somewhat higher than 20 per cent at 30 kv. accelerating potential for the bombarding electrons. The relative energy distribution of the light, emitted by this phosphor under electron bombardment, is shown in Figure 7, curve a (solid line). Curve b (dotted line) of the same figure shows the eye response curve for comparison. It can be seen that the light emitted by the viewing screen phosphor matches favorably the sensitivity of the human eye.

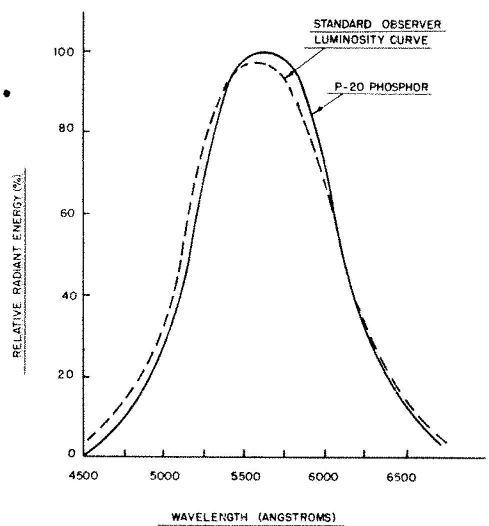

Fig. 7. Relative radiant energy of the viewing screen phosphor and the eye-response curve.

The yellow-green ZnS phosphor may also be matched favorably with proper photographic material such as Tri-X. Proper matching is most successfully obtained if the brightness of the viewing screen is relatively low, namely, 1 to 10 FL. For higher brightness values, 50 FL and more, the maximum in the relative radiant energy distribution shifts slightly towards longer wavelengths and the emitted light becomes subjectively more yellow. This relatively high brightness range is, however, hardly of any importance for image intensifier fluoroscopy and roentgenoscopy.

The resolution obtainable on a settled phosphor screen is ultimately determined by the size of the phosphor particles or the size of the particle conglomerates. The most probable particle size of the bulk phosphor used is 5 μ. This value is reduced by elutriation to approximately 2 μ. Experience has shown that a minimum resolution of 1,000 television lines per inch (500 line pairs per inch—500 optical lines per inch) can be realized readily with such a particle size.

The viewing screen is aluminized to increase the light output, to avoid local charging and to protect the ZnS phosphor against attack by the Cs vapor which is present during processing of the photocathode.*

PHOTOCATHODE

An SbCs photocathode is used. The spectral sensitivity of the semitransparent photosurface matches favorably the spectral emissivity of the blue pickup phosphor used. Further, the quantum efficiency of this photosurface is higher than the efficiency of most other surfaces with the exception of the multi-alkali surface. As the SbCs surface is more easily controlled in mass production than the multi-alkali surface, an SbCs photocathode has been selected. Such a photocathode consists of a thin, amorphous antimony base layer which, reacting with Cs vapors at the processing temperature of 100–170°C. is converted to a layer of the intermetallic

* It is known that most sulfide phosphors are inactivated by the influence of Cs vapors. Silicate phosphors do not display this effect.

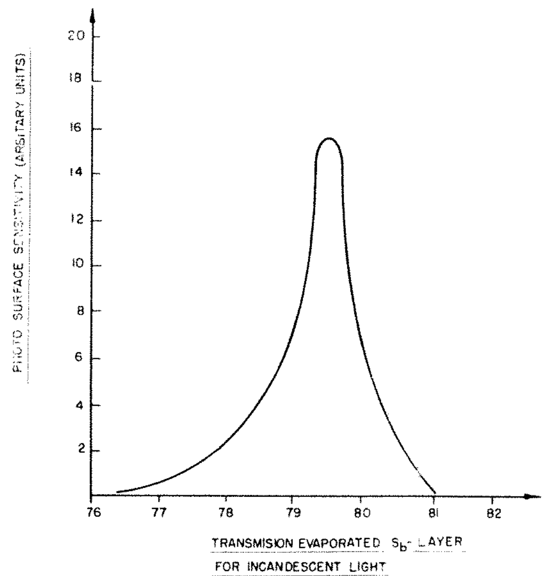

FIG. 8. Thickness of the Sb base layer and photosurface sensitivity.

compound Cs_3Sb. Finally, free Cs molecules, embedded in this layer, are permitted to react with free oxygen brought into the tube to form the final photosurface.

In semitransparent photocathodes, electromagnetic radiation impinges onto the photosurface from one side and photoelectrons are emitted from the opposite side. It is known that photoelectron emission is co-determined by the balance between absorption of light quanta and the depth of photoelectron generation. Thus, the thickness of the photoemissive layer is important. The influence of the thickness of the Sb base layer on the sensitivity of the photosurface used in the intensifier is shown in Figure 8.

ELECTRON OPTICS

Point Symmetric System. The electron-optical system used in the x-ray image intensifier consists of a spherical cathode, spherical pierced anode, and cylindrical focusing electrode. A simpler system, showing imaging properties similar to the system applied in practice, will be discussed first.

Let us consider an electron optical system consisting of two concentric, spherical electrodes: the outer larger sphere is the cathode and the inner smaller sphere is pierced and forms the anode (Fig. 9). The parameters of such a system governing its performance are as follows: with R_C as the cathode radius and R_A as the anode radius, $n = R_C/R_A$; with D_A as the diameter of the aperture in the anode sphere, T_A as the thickness of the anode aperture, and d_{AV} as the distance from the outside of the anode sphere to the image plane, $k = D_A/R_A$. Note that the anode voltage is not included in these parameters. The equations governing the performance of such a system have been derived by Schagen, Bruining and Francken[5] and shall be given without proof. The following assumptions are made: (a) that the image is gaussian, (b) that both cathode and anode are complete spheres, and (c) the anode aperture lens is subjected to the usual assumptions validifying the application of the Davisson-Calbick formula.

Under these assumptions, an object on the cathode is imaged onto a spherical image plane (concave as seen in the direction of electron propagation) whereby the image distance (axial spacing between anode aperture and image plane) is given by:

$$d_{AV} = R_A \left[\frac{1}{n} \cdot 2(n-1) - (n-1)/(n-2) - k/\pi \right] \Big/ 4 \frac{n-1}{n-2} \left(\frac{n-1}{n} - \frac{k}{2\pi} \right) \quad \text{(9a)}$$

Assuming a very small anode aperture diameter, Equation 9a simplifies to ($k/2\pi \ll 1$):

$$d_{AV} = R_A \cdot 4(n-1)/(n-4) \quad \text{(9b)}$$

The resulting image might be either magnified or demagnified, depending on the selection of both the cathode and anode radius.

The curvature of the spherical image plane is $1/d_{AV}$. As the viewing screen in a practical tube is flat (to minimize distortions by image pickup with a light optical system), resolution loss in the peripheral area results, combined with pincushion

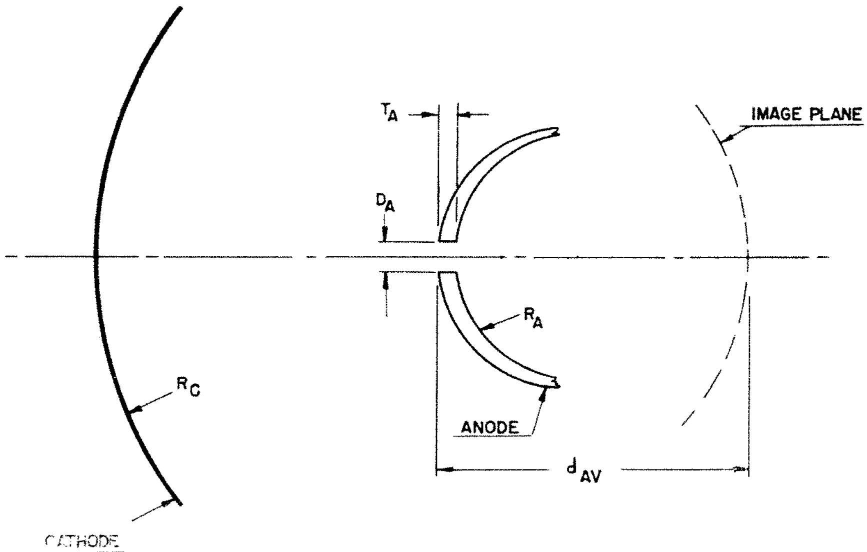

FIG. 9. Point symmetric electron optical system with pierced anode.

distortion. These distortions decrease with d_{AV} increasing.

An increase of the image distance can obviously be obtained by increasing the strength of the (negative) aperture lens (pierced anode sphere). The strength of this lens is increased by increasing T_A, the thickness of the material forming the anode aperture. However, this correction does not change d_{AV} as function of the radial distance of a peripheral object point. Such a correction is, however, required to obtain a nearly complete flattening of the image plane. For this reason, the anode aperture lens is discussed in more detail in the following paragraphs.

*Anode Aperture Lens.** The equations given in the above section treat the anode aperture lens under the usual assumptions, namely: (a) restriction to paraxial rays; (b) thin lens approximation (this means that the influence of the potential in the center of the anode aperture extends to both sides of the aperture, a distance appreciably smaller than the aperture radius); and (c) normal ray incidence (zero angle between the incident ray and the axis of the lens).

* Mr. I. Csorba, of the Rauland Corporation, assisted in obtaining the results discussed under this heading.

The change in strength of the aperture lens with increasing radial spacing r can be discussed qualitatively by adapting the analytical expression for the axial potential $V_0(z)$ in a system consisting of an aperture enclosed by two parallel planes to the anode aperture considered here:[6]

$$V_0(z) = \frac{V_A}{d_{1,2}}\left[\frac{2R}{\pi}\left(\frac{z}{r}\operatorname{arc\,tg}\frac{R}{2} - 1\right) + \frac{z}{2} - |z| + d_{1,2}\right] \quad (10)$$

where r = radial coordinate, z = axial coordinate, $d_{1,2} = R_C - R_A$, and $R = D_A/2$. The potential in the paraxial and (in approximation) marginal space can be obtained by applying the integral solution of the LaPlace equation in series development:

$$V(r, z) = V_0(z) - \frac{V_0^{\mathrm{II}}(z)r^2}{2^2} + \frac{V_0^{\mathrm{IV}}(z)r^4}{2^2 \cdot 4^2} \pm \quad (11)$$

For evaluation of the above equation, the second and forth derivatives of the axial potential are given below:

$$V_0^{\mathrm{II}}(z) = -\frac{2V_A}{d_{1,2}}\left[\frac{R^3}{(z^2 + R^2)}\right] \quad (12a)$$

$$V_0^{\mathrm{IV}}(z) = -\frac{8V_A}{\pi d_{1,2}}\left[\frac{5z^2 - R^2}{(z^2 + R^2)^3}\right] \quad (12b)$$

The field strength on both sides of the anode aperture with the origin of a cylindrical coordinate system placed in the center of the aperture follows (with positive values of z in the direction of electron propagation):

$z > 0$:

$$E_{z,2} = \frac{V_A}{\pi d_{1,2}}\left[\operatorname{arc\,tg}\frac{R}{z} - \frac{zR}{z^2 + R^2}\right] \quad (13)$$

$z < 0$:

$$E_{z,1} = \frac{V_A}{\pi d_{1,2}}\left[\operatorname{arc\,tg}\frac{R}{z} + \pi - \frac{zR}{z^2 + R^2}\right] \quad (14)$$

and we obtain:

$$E_{z,2} - E_{z,1} = -\frac{V_A}{d_{1,2}}\left[1 + \frac{6z}{\pi r} + \frac{z}{2\pi R^2}\right] \equiv A \quad (15)$$

If $r \gg z$, the axial field strength difference is obtained with:

$$E_{z,2} - E_{z,1} = -\frac{V_A}{d_{1,2}}\left[1 + \frac{2z}{\pi R}\right] \equiv B \quad (16)$$

The ratio A/B gives a correction for the focal length as a function of radial spacing:

$$A/B = \left[1 + \frac{6z}{\pi R} + \frac{z}{2\pi R^2}\right] \Big/ \left[1 + \frac{2z}{\pi R}\right] \quad (17)$$

Note that the focal length f_R for limiting case in the marginal space is now expressed (with f_0 as the focal length in the paraxial space) by:

$$f_R = (B/A)f_0 \quad \text{with} \quad B/A < 1 \quad (18)$$

It follows that the focal length decreases with increasing radial spacing. The decrease of the focal length becomes more pronounced if the rate of the radial potential increase increases. This means that the increasing strength of the negative lens leads to an increasing image distance with increasing radial spacing. This effect may be utilized in practice by selecting an anode aperture sufficiently small so that the aperture lens is filled entirely by the electron beam.

A further correction for the peripheral defocusing will be considered now on a phenomenologic basis. The above equations assume normal beam incidence in the anode aperture lens. However, in the actual case, the rim rays might show an angle of incidence larger than zero. This is particularly the case if the cathode and anode spheres are not concentrical and if the anode is pushed towards the cathode or:

$$\text{axial spacing cathode to anode} < R_C - R_A \quad (19)$$

It is known that the Davisson-Calbick formula for spherical apertures can be modified for an angle of incidence larger than zero:

$$f_{0,\alpha} = \frac{4\Phi_0}{\Delta E_z}\cos^2\alpha \quad (20)$$

with $f_{0,\alpha}$ as the paraxial focal distance (for $\alpha > 0$) and Φ_0 as the potential in the center of the anode aperture. We may assume as a first approximation that the focal distance f_R for the rim rays is modified in a similar way, thus:

$$f_{R,\alpha} = f_R \cos^2\alpha \quad (21)$$

One can see that the strength of the negative anode aperture lens increases with the increasing angle of incidence of the rim rays. Thus, the image plane for the rim rays with $\alpha > 0$ shows a larger spacing from the anode aperture than the image plane for the zonal rays having approximately normal incidence.

This effect, similar to the effect of changing lens strength with increasing radial spacing and normal incidence, flattens the electron optical image plane as a function of the radial distance of a peripheral object point and facilitates receiving of the obtained real image on a physically flat plane.

The application of both corrections to a practical electron-optical system is discussed in the following paragraphs.

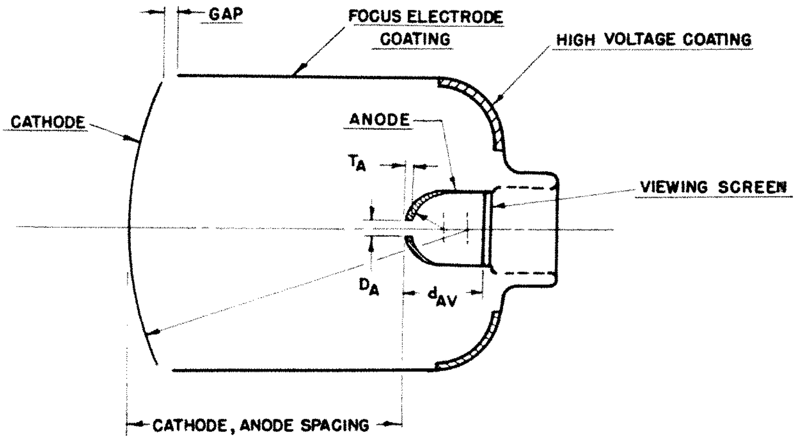

Fig. 10. Pseudo-point symmetric electron optical system.

Pseudo-Point Symmetric System. A strictly point symmetric system, as outlined under *Symmetric System* above, cannot be realized in a practical tube design. Thus, the practical electron-optical system used in the large diameter x-ray image intensifier tube consists of a spherical cathode (C), a spherical pierced anode (A) and a cylindrical focus electrode coating (F) terminated by a semiconductive wall coating (S) (Fig. 10).

The cathode-anode distance d_{ca}, measured axially, is smaller than the difference of the radius of curvature of cathode and anode. The semiconductive coating is terminated on one end by the focus electrode coating and connected electrically to the anode voltage. Thus, the wall potential along the section of the tube envelope covered by the semiconductive coating depends on both the potential difference between the focus electrode and the anode and the resistance properties of the semiconductive coating.

The main purpose of the focus electrode coating is to correct for the finite extension of both the cathode and the anode. Changing the focus electrode voltage (which is approximately equivalent to changing the potential difference between focus electrode coating and cathode) influences both the focal distance of the entire system and the size of the reproduced image. Peripheral defocusing in the image, caused by the spherical curvature of the electron-optical image plane, has been compensated for in the following manner:

(a) The strength of the negative anode aperture lens has been selected as a compromise value by choosing a proper thickness for the material forming the anode aperture (the wall thickness of the material forming the aperture is less than the diameter of the aperture); thus, the radius of curvature of the electron-optical image plane is somewhat increased or the image plane is flatter.

(b) The cathode and anode spheres are not concentric; thus, rim rays emitted from the cathode enter the anode aperture lens in the marginal region under an angle of incidence larger than zero. The image plane flattening effect of this measure has been described in the previous section.

(c) The semiconductive wall coating causes the curvature of the equipotential planes in the neighborhood of the anode aperture to decrease successively in the direction of electron propagation. This effect causes a successive increase in the angle of incidence for the rim rays, the effect of which on the image plane curvature has been mentioned above.

(d) The electron beam fills the entire anode aperture; the image distance for the rim rays is greater than for the paraxial rays, as mentioned above.

Thus, the electron-optical system dis-

cussed here possesses a flatter image plane than an electron-optical system where the focus electrode coating has the sole purpose of compensating for the finite extension of cathode and anode.

FOCUS ELECTRODE COATING AND HIGH VOLTAGE COATING

The focus electrode coating should be nonreflective for the blue light of the pick-up screen which penetrates the semitransparent photocathode, particularly if the coating extends appreciably into the "shoulder region" (Fig. 3), as back reflection of the blue light to the photocathode would result in spurious electron emission reducing the obtainable contrast. Copper, among other materials, shows the property of low reflectivity in the blue band and can be used as a material for such a focus electrode coating. However, an evaporated copper coating suffers generally from a copper oxide interface layer between the glass substrate and the copper. These copper oxides break down at approximately 250°C. at $10^{-4}-10^{-5}$ mm. pressure, thus endangering the cleanliness of the tube and the photosurface sensitivity. In addition, the adherence of an evaporated copper coating to glass is rather poor.

An evaporated aluminum coating, appreciably simpler in production than an evaporated copper coating, can be used if at least the shoulder region of the tube envelope (Fig. 1) is coated with nonreflective material. As the high voltage coating mentioned above is nonreflective in the blue band, the combination of an evaporated aluminum coating on the cylindrical portion of the tube envelope with a proper semiconductive coating in the shoulder region not only approaches the reflection properties of a copper coating alone, but it also renders the tube more practical for mass production.

The semiconductive high voltage coating yields lower values for the local potential gradient along the glass wall between the low potential focus electrode coating and the high potential anode contact, rendering the tubes operable for anode voltages in excess of 45,000 volts. These voltage values can be regarded as being higher than normally encountered in image converter tubes.

The purpose of the high voltage coating may be summarized as follows: (a) establishing the proper wall potential to obtain a flatter image plane; (b) increasing the threshold for high voltage breakdown and local field emission; and (c) reducing the reflectivity for the blue light emitted by the pickup phosphor.

PERFORMANCE OF THE LARGE DIAMETER X-RAY IMAGE INTENSIFIER

STANDARDIZATION OF MEASUREMENTS

As the field of x-ray intensification is a relatively new one, no generally accepted standard for determining performance parameters such as brightness gain, resolution, etc. exists as yet. One of the reasons for this situation may be the inherent difficulty of defining the input energy. Practically all performance parameters depend on the geometry of the test gear, namely, spacing between x-ray generator and image intensifier, divergence of the x-ray beam, etc. Further, the type of x-rays used, namely, wavelengths (anode voltage of the x-ray tube), wave form of the high voltage applied to the x-ray tube (half wave rectified, full wave rectified with ripple, "constant" voltege), etc. is of great importance.

If not mentioned otherwise, all tests were carried out under the conditions and with equipment as described below:

X-Ray Unit. Picker U. S. military unit, type T55-35, 110 volts AC, 60 cycles input, x-ray tube voltage half wave rectified, standard operation 80 kv. peak, 2 ma.

Geometry of the Test Gear. Axial distance x-ray window of image intensifier tube to x-ray focal point, 25″, meshes and phantoms touching the dome of the image intensifier.

Phantoms. Size: 12″×12″ bakelite, lead markers used for 1″ and ½″ divisions orientated in the form of a cross. Resolution: woven meshes, 12″×12″, mounted between

plexiglas sheets, diameter of circular brass wire .012″—.008″. Contrast-detail phantom: plexiglas phantom with holes of constant diameter and varying depths in one direction and holes of constant depth and varying diameter in the other direction (normal to above direction).

Brightness Meter. Spectra Brightness meter, Model UB-1½, Photo Research Corporation.

Telescope. Gaertner Scientific M508, angular magnification 20 times at 140 mm. diameter of object field.

Magnetic Shielding of the Image Intensifier. Mumetal shield, 1/16″ thick, enclosing the image intensifier from the Kovar flange (Fig. 3) to the anode, open on both sides.

In the following sections we shall discuss each one of the performance parameters in detail and describe the measurement techniques.

BRIGHTNESS GAIN

As mentioned above, the brightness gain of the x-ray I.C. depends on both the geometric minification of the tube and the genuine flux gain due to electron acceleration.

As the size of the output image depends somewhat on the focusing voltage, the x-ray I.C. is first adjusted for proper focus voltage at the operational high voltage by using a resolution mesh. Then the resolution mesh is removed and a 20 mm. thick solid pure aluminum phantom is inserted between the x-ray window of the image intensifier and the x-ray tube. The x-ray attenuation of the aluminum phantom is comparable to the x-ray attenuation of the average human chest.

The brightness of the viewing screen is measured at 80 kv. peak, 2 ma., x-rays after an excitation of at least 10 seconds.

Thereafter, the x-ray image intensifier is removed and a Patterson CB-2 screen* is inserted at the location of the intensifier pickup screen. The brightness is again determined under identical x-ray intensity and measurement conditions. Then, the brightness gain is obtained by dividing the brightness on the viewing screen of the x-ray image intensifier by the brightness of the Patterson CB-2 screen. A minimum brightness gain of 1,000 is guaranteed. The most probable brightness gain is around 1,500 and considerably higher values have been obtained.

* The Patterson CB-2 fluoroscopic screen has almost the same relative radiant energy distribution as the viewing screen phosphor of the image intensifier.

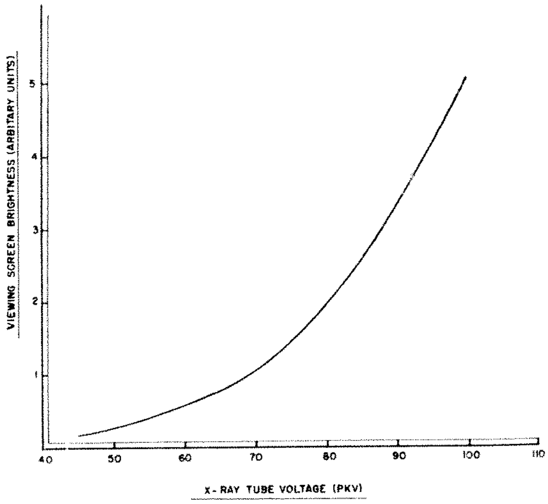

FIG. 11. Brightness of the viewing screen as function of the x-ray tube voltage.

The brightness gain of the tube (or the brightness of the image on the viewing screen) is approximately flat with increasing x-ray hardness (decreasing x-ray wave lengths) between 75 kv. peak and 110 kv. peak as shown in Figure 11. Thus, the tube can be used successfully in the normal x-ray range encountered in medical and also in industrial radiology.

The brightness on the viewing screen depends further on the anode voltage applied to the x-ray image intensifier, as shown in Figure 12. It can be seen that the brightness versus anode voltage curve increases around 30 kv. anode voltage. However, the rate of increase decreases beyond approximately 33 kv. This means that the minimum required thickness of the viewing screen at the operational anode voltage has been selected. A greater thickness of the viewing screen might lead to a resolution loss.

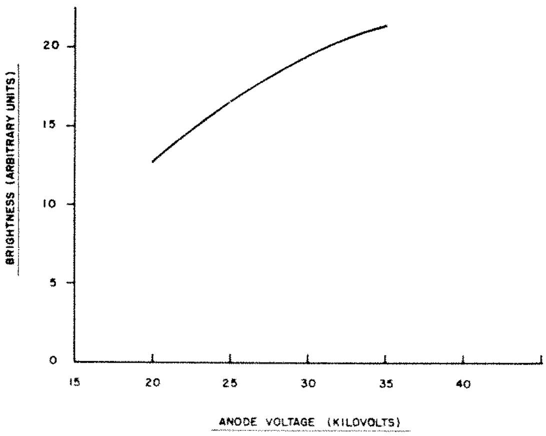

Fig. 12. Brightness of the viewing screen as function of the intensifier anode voltage.

The brightness gain values discussed here have been obtained at a nominal minification of 7.5.

RESOLUTION

By "resolution" is meant the limiting value of the contrast-detail perceptibility curve for contrast values approaching 100 per cent.

The resolution is determined under the conditions described in the section, *Standardization of Measurements*, above, at the operational x-ray brightness level (but with an aperture of 0.3 mm. at the x-ray tube). This means the x-ray tube is adjusted to 80 kv. peak and 2 ma. and the 20 mm. aluminum phantom is used between the resolution mesh and x-ray tube. The resolution mesh is inserted between the x-ray window of the intensifier and the aluminum phantom with as close spacing as possible.

A resolution of 80–100 television lines per inch is achieved on the pickup screen across a central area with a diameter of approximately 85 per cent of the total useful pickup screen diameter. The peripheral resolution is equal or greater than 55 television lines per inch with the focus voltage adjusted for optimum resolution in the central area.

A certain amount of pincushioning, resulting from the projection of the somewhat curved electron-optical image plane onto the flat viewing screen and the flat phantom onto the curved pickup screen, is unavoidable. Figure 13 shows the photograph of wire mesh imaged onto the viewing screen of the intensifier tube, to illustrate pincushion distortion. The photograph has been made under the condition as described above.

PICKUP SCREEN DIAMETER AND IMAGE SIZE

Both the pickup screen diameter and the image size depend somewhat on the focusing voltage. Thus, the pickup screen diameter is determined with the size phantom (see above) and a resolution mesh is inserted as close to the x-ray window of the intensifier tube as possible. Then the image intensifier is adjusted for proper focusing and the lead markers of the size phantom are counted in the reproduced image.

As mentioned above, a slight geometric magnification must be taken into account caused by the divergence of the x-ray beam and the unavoidable physical spacing between the flat size phantom and the edges of the curved pickup screen. Thus, the actual phantom diameter is slightly smaller than its shadow image on the pickup screen. For a typical medical x-ray set-up as described above and the size phantom practically touching the x-ray window of the tube, the geometric magnification value amounts to approximately 1.1.

The usable pickup diameter is $8\frac{1}{2}$ inches. The image diameter can be determined experimentally by a simple measurement (average value 1.15).

SPEED OF RESPONSE

The speed of response is measured with a photomultiplier pickup (S-11 surface, head-on multiplier) and a DC-oscilloscope under the test conditions previously described. The 20 mm. aluminum phantom is inserted between the window of the image intensifier and the x-ray tube, and the x-ray tube is operated at fully rectified high voltage ("constant voltage"). The decay is determined after an x-ray excitation period of at least 10 seconds. The brightness of the output phosphor decreases to 5 per cent of the

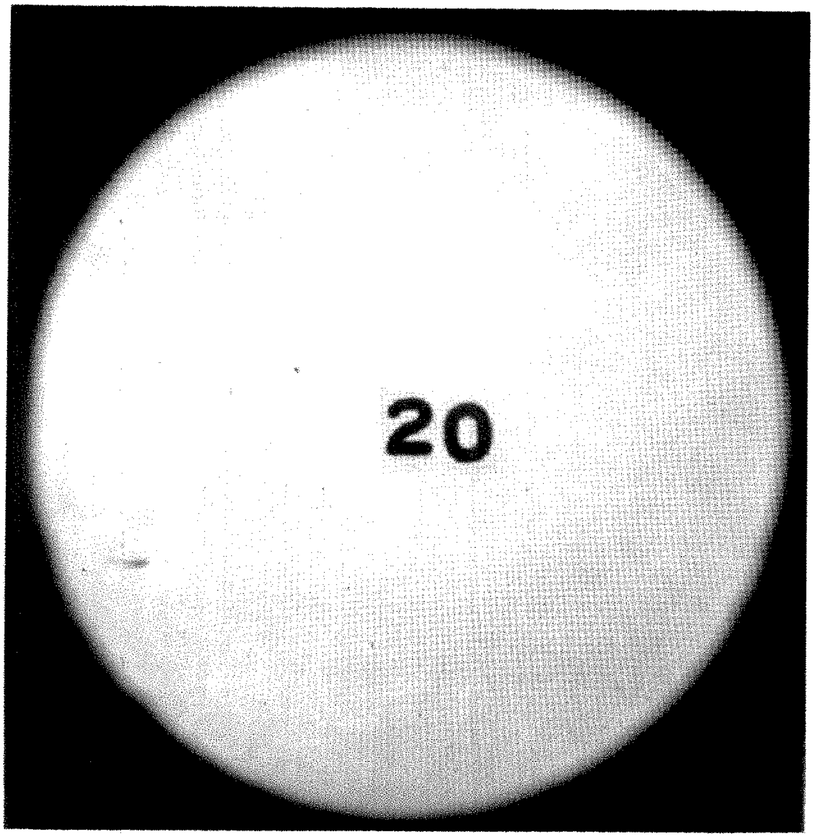

FIG. 13. Photograph of a mesh phantom showing the pincushioning effect in the peripheral area.

original brightness within 0.2 seconds (Fig. 14). This speed of response is sufficiently fast so that no limitation is imposed on the use of this device in medical fluoroscopy (with and without scanning of the subject with the intensifier tube), radioscopy and cinefluoroscopy as well as television fluoroscopy.

As the speed of the pickup phosphor depends on the duration of x-ray excitation, the decay of the image intensifier for 60 sinusoidal half cycles per second x-ray excitation is so fast that the brightness of the output phosphor decreases to practically zero between the half cycles. Thus, the device is very well suited for relatively fast response, pulsed x-ray operation.

CONTRAST-DETAIL PERCEPTIBILITY

As mentioned at the beginning of this paper, contrast and detail perceptibility are connected by the simple relation,

$$C = (B_2 - B_1)/B_1 = k/\sqrt{N} \quad \text{(Equation 1)}.$$

For small values, the contrast C can be expressed by:

$$C = ln\ (B_1/B_2) \tag{22}$$

It is convenient in using a contrast-detail phantom, as described under *Standardization of Measurements*, to express the contrast C by thickness of the material penetrated by the x-rays. Realizing that the x-ray attenuation follows an exponential law with the attenuation coefficient K in the exponent, we obtain for C:

$$C = K\Delta d \tag{23}$$

whereby Δd represents the difference of the full material thickness of the phantom and the thickness of material remaining in the holes (or the depth of the holes).

Contrast-detail perceptibility curves have been determined with the phantom in-

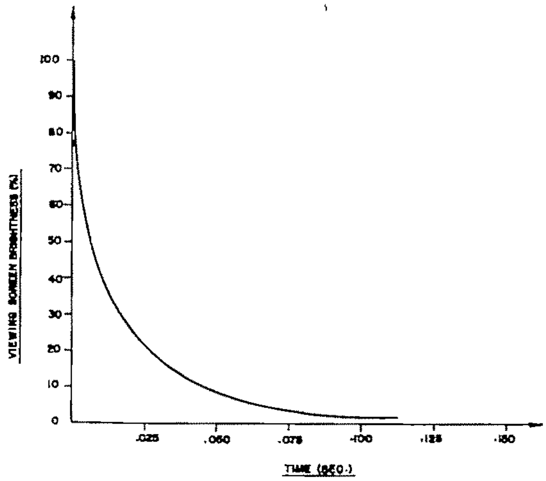

FIG. 14. Decay of the viewing screen brightness.

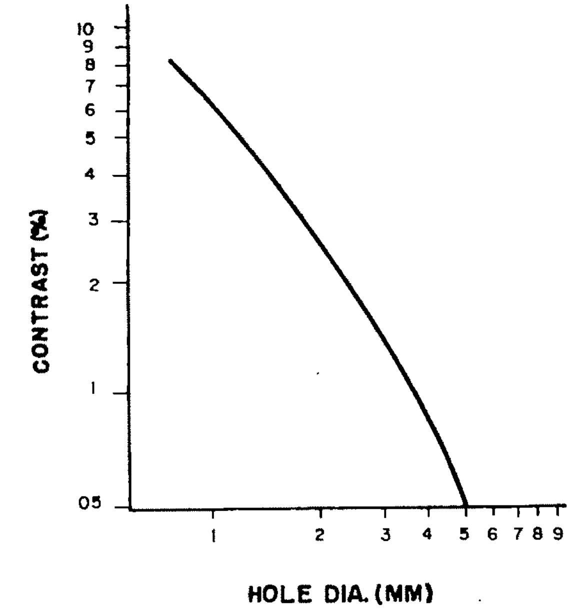

FIG. 15. Contrast-detail perceptibility curve.

serted between the window of the image intensifier and the 20 mm. aluminum phantom under 80 kv. peak, 2 ma., (half-wave rectified) x-ray excitation. The geometric setup was equal to that described under *Standardization of Measurements*. A typical curve is shown in Figure 15.

SUMMARY AND CONCLUSION

X-ray image intensification permits a reduction of the radiation doses in fluoroscopy as well as the application of cinematography and television techniques to medical radiology.

X-ray intensifying systems, namely, electronic, solid state and vacuum tube systems, are surveyed and the conclusion is reached that only vacuum tube systems have been developed to such a technical maturity as to permit successful practical application.

The design of a large size vacuum tube x-ray image intensifier (cathode diameter $8\frac{1}{2}$ inches, minimum brightness gain 1,000) is described. Structural details such as the cross-section profile of the x-ray window, location of the pickup screen and linearity distortions, etc. are discussed.

Further, the imaging by the electrostatic triode system, used in this tube, is analyzed mathematically with special emphasis on the properties of the negative anode aperture lens and the curvature of the image plane of such a system. The concept of a "pseudo-point symmetric system" is outlined together with the function of the "high voltage coating," a new electron-optical element for structure of this type.

Performance data of the large size x-ray image intensifier are listed in detail together with a thorough description of the measurement techniques used.

In conclusion, it can be stated that the x-ray image intensifier tube described here is universally applicable to medical radiology and may also be used to advantage in the field of industrial x-ray techniques.

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The development of a system incorporating a novel component necessitates cooperation between several companies as well as the forming of scientific teams within those companies. Thus, it is hardly possible to give credit here to all those persons who are entitled to it.

Corning Glass Works, Corning, New York, and Kimble Glass Company, Toledo, Ohio, deserve credit for services rendered in the development of the glass envelope of the intensifier tube. The Picker X-ray Corporation, Waite Manufacturing Division, Cleveland, Ohio, developed the x-ray equipment on which the x-

ray image intensifier is used and carried out invaluable work in evaluating the performance of sample tubes. Dr. J. Ball and Mr. E. B. Graves were especially helpful in this respect.

I am greatly indebted to Dr. C. S. Szegho, Director of Research of The Rauland Corporation, for continuous guidance and encouragement in developing the intensifier tube. Mr. A. Schmidt and Mr. H. Jordan assisted substantially in solving many chemical and mechanical problems. Finally, the Glassblowing Shop of The Rauland Corporation, under the supervision of Mr. H. Voelz, deserves credit for developing the first experimental glass envelopes.

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TELEVISION CINEROENTGENOGRAPHY: DOSE AND CONTRAST FACTORS*

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THAT a television system can give a large bright multiple image remote from scattered radiation is well known. The use of roentgen rays in conjunction with television to reduce the dose to patient and physician was patented by the Frenchman, A. Dauvillier, in 1915, and the system was demonstrated by him in 1928. Besides the advantage of requiring minimum dark adaptation from the viewers, such systems can provide image brightening over a wide subject field. They can give reasonable contrast at high voltages where some intensifiers are ineffective because of the direct activation of the rear phosphor by the penetrating rays. In cineroentgenography a given image quality can often be produced with less dose by using television techniques, and this aspect will be discussed here.

Much has been written and said about roentgen-ray detectors and, of course, they are the heart of any such system. In the present paper the detector will not be considered, but only how to systematically make the best possible use of the one available. The discussion will hold for any detector that shows storage, *i.e.*, in which the effect of each interacting quantum is added to that of all the previous until a scanning process removes the accumulated information at any one point in a single signal. Commonly used examples of such detectors are the vidicon and the image orthicon, used with or without a preceding image intensifier, upon which is focussed the image of a fluorescent screen, and the roentgen-ray sensitive vidicon, which is a semiconductor device directly sensitive to roentgen rays.

In rendering a roentgenographic image visible, roughly the same number of increments from light to dark are discernible photographically as with television. But with television, emphasis can be concentrated to study one small range in detail. However, a large roentgenogram can contain detail corresponding to a band width in the hundred megacycle range at normal frame rates (Appendix 1) and its grain can be somewhat less troublesome than the noise characteristic of most detectors at low levels. A discussion of film and television methods has been given.[1] Film and electronic detectors can show similar quantum efficiencies. Thus television procedures can be advantageous; but to maximize information transfer and minimize dose, one must also consider the television link and camera. For example, nonlinear circuits can enhance contrast and make detail more noticeable. One can sometimes see more in a television image than by direct viewing.

CONTRAST

Contrast (taken as the percentage change in intensity at a boundary of a given structure) in the original unconverted roentgen-ray image depends not on roentgen-ray intensity but on roentgen-ray wave length distribution. This may be monitored with a scintillation detector and the gray wedge pulse height analyzer shown in Figure 1. Each interacting quantum has its energy recorded. Because of the multichannel action, this unit can give a spectrum from a tube running under normal operating conditions without requiring an exposure time comparable with the tube life. Various machines can thus be adjusted to give comparable outputs. It is also suitable for use under low intensity conditions such as in evaluating beam hardening on traversing a patient (assessing the outcoming spectrum). An example of the result is shown in

* From a paper presented at the Second International Medical Electronics Conference, Paris, France, June, 1959.

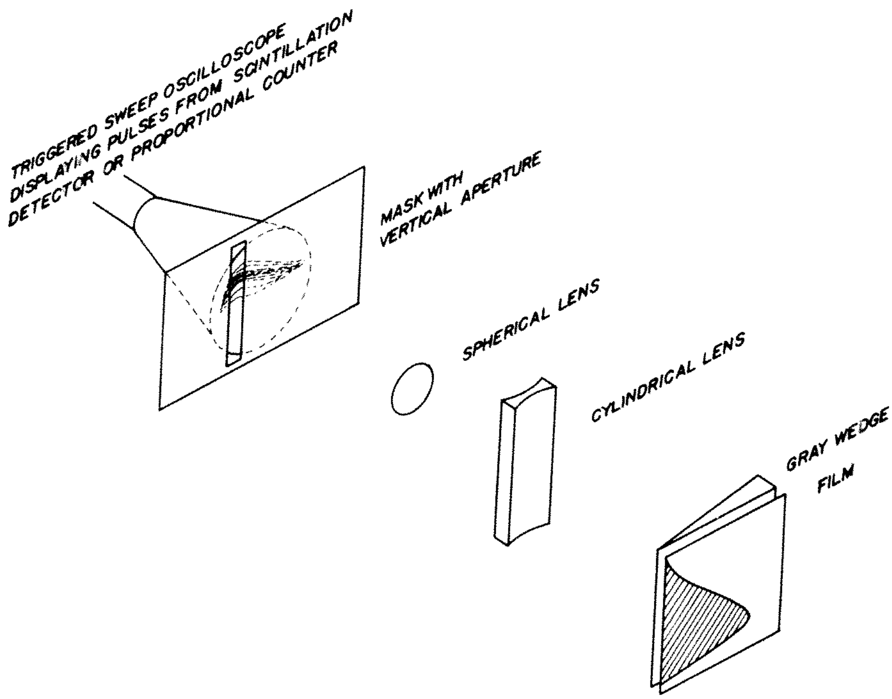

FIG. 1. The peaks of the pulses form a vertical column of bright spots which are spread by the lens system into horizontal lines, one above the other. The film will be blackened, to a given degree, farther to the right at a level where several pulses occur with the same height due to several quanta of one energy entering the detector. The spectral distribution appears directly on the film and curve shape does not depend on the linearity of the film or phosphor. The wedge can be replaced by a triangular diaphragm, or the cylindrical lens can be eliminated by using the expanded or fast delayed sweeps on certain oscilloscopes. Nonuniformities in the phosphor or optical system can be compensated for by placing before the film a mask made by exposing a negative while there is a vertical line on the screen. In general, this seems unnecessary.

Figure 2. Such absorption spectroscopy should allow composition analysis, thus making roentgenography more quantitative, and it should also provide maximum contrast images (Appendix II).

•When the television image is photographed, film density need not be a function of roentgen-ray intensity or dose since the television output can be brightened arbitrarily. Structure may be better defined than in direct exposure since with a television detector a given blackening can be due to many absorbed quanta rather than many progeny per interaction. Too many or too few progeny per absorbed quantum are both bad. In one case the film can be black before detail is defined[2] and in the other there is no visible image with reasonable dose. With television the dose demanded can depend only on the detail to be resolved and image detail corresponding to any dose level can be recorded (subject to detector limitations) since the sensitivity of the recording medium need not be considered in choosing the exposure.

Usually, if the over-all response of the television system is such that when output brightness is plotted as a function of input intensity, as in Figure 3, the resulting curve is concave upward, then contrast is enhanced. Subtle details can become more noticeable.[2] The over-all response can readily be changed by a biased-diode electrical network. Even if the circuits are linear, the over-all response will usually be of the above character because many cathode ray tubes give an output that is proportional to approximately the 2.5 power of their input voltage. If photography is used in rendering the roentgen-ray

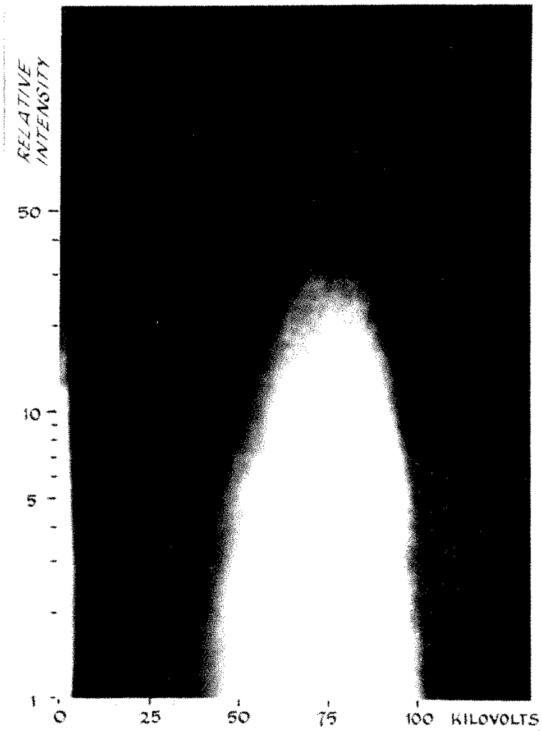

Fig. 2. Energy distribution as presented by scintillation detector and pulse height analyzer. The roentgen-ray source was a tungsten target tube fed by an unfiltered full wave rectifier set at 100 kv. The beam was filtered by 0.5 mm. of aluminum and 7 m. of air. Approximately 4,000 quanta interacted with the detector in less than one half second. Detectors do not show perfect resolution, but in this energy range they are not troubled by Compton interactions or pair production. If more quanta are used to give a smoother curve then it should prove possible to employ an optical computer based on filtering spatial frequencies to correct the observed distribution for imperfect energy resolution.

image visible, then film nonlinearity is also involved. These nonlinearities can be augmented electrically to make saturation transitions more abrupt outside the range of interest.

Precisely, contrast is enhanced if the tangent to the response curve crosses the axis to the right of the origin.[2] In Figure 3 are seen some examples of contrast altering responses. An electrical bias or ambient illumination can lead to a sharply rising characteristic at the origin. A large slope in the region of interest is required to notice subtle detail. To detect a tiny signal when there is a threshold sensitivity requires a high slope near the origin. The simple curve that gives this is concave down. This is the case in radar work[6] and it can sometimes be applicable in radiology. To best use the remainder of the dynamic range, a concave up region might then follow the threshold level. It can be shown that an equivalent criterion for contrast enhancement requires that the slope on a log-log plot be greater than unity (Appendix III).

An undetectable gradient may sometimes be noticed if it is moved or in motion. (For example, one can sense the motion of interference fringes that one cannot see.) This not only suggests another way for studying roentgenograms, but it also indicates that more may be visible in a movie than in a set of stills with the same contrast.

MOVING PICTURES

If one uses a standard sound camera (24 frames per second) to record the image as in standard television practice (30 frames per second, two field per frame interlace), then dose will be 2.5 times that necessary to produce the given image quality and resolution will only be approximately half that potentially present. The former is due to the camera shutter being closed for three fifths of the time, and the latter because successive fields do not appear on the same or on successive movie frames and after projection there is little chance of interlace. Because of storage effects in the detector, dose is not reduced if the roentgen-ray beam is turned off whenever the shutter is closed, but there will then be a 4-to-1 exposure difference across each frame. Interrupting the detector scan is usually preferable to and easier than interrupting the roentgen-ray beam. In order to avoid loss of information or excess dose, one must employ either a shutterless recorder with continuously moving film, or a camera with "instantaneous" film advance. The problem is not that the patient is irradiated while the shutter is closed but rather that

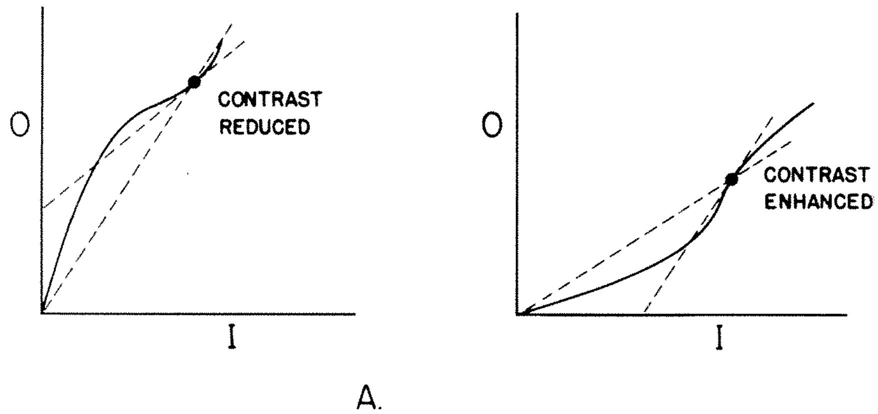

FIG. 3. Examples of response of a television system: visible light directed into eye versus input roentgen-ray intensity from subject. These characteristics are sketched with an inflection point. Though unusual, contrast can be enhanced in a range where the transfer function is concave downward, or decreased when it is concave upward, depending on the slope of the tangent at the point compared with the slope of the line drawn to the origin.

the detector is being scanned and erased at that time. One can consider many cycles of storage and recording in which there is time for a normal film "pull down," but most have some fault, one of the more common being loss of uniformity due to asymmetry in storage when different sections are returned to after different storage times. Mechanically, the continuously moving film camera seems the most durable.

A continuously running film camera photographing a short-persistence phosphor (P 16) on a cathode ray tube with no vertical deflection need lose the effect of no interacting quantum. Camera frame height can be changed by applying attenuated forward or reverse vertical sweeps to the output tube. Frame width can be controlled by camera distance. In principle, two-field-per-frame interlace can be retained if there is a full verticle sweep in full *frame* time on the output tube. A particular phase is not necessary in starting the film since this only requires adjusting the projector gate. However, in the present apparatus a tiny phototube in the camera generates an impulse each time a sprocket hole in the film passes a fixed point. This signal triggers each television frame start for stability and also fixes the starting phase. Feedback from a roller in the film loop can also be used to control the cathode ray line position if there is a tendency for the image to drift. To prevent phosphor burn, the output tube is turned off when the roentgen-ray beam is off, and tube elevation is periodically altered. Sprocket hole feedback is also used to trigger a flash tube to record auxiliary dials (*e.g.*, clocks and pressure gauges) directly on the film. The camera used in the present studies was made in the fashion of some magnetic tape recorders, but presumably one could use a commercial rotating-prism camera after removing the prism.

Because of storage in one's visual system, the dose is relatively independent of the frame rate if each frame need not be suitable for individual study. Any decrease in the viewing relative to the taking rate increases the required dose. If in clinical study one wished to concentrate on a single frame at a time, then the roentgen-ray beam current would have to be turned higher, proportional to frame rate, so that each frame alone would contain an adequately detailed image. In this case dose increases proportional to frame rate and one should take frames at the lowest rate that will record the motion involved. There should be no movement between two frames that is more than, say, one third the finest expected dimension of interest. If

one wishes to stop any blurring, the image can be laid down with a short roentgen-ray pulse once per frame. On the other hand, steady irradiation at a lower rate during the whole frame allows one to learn, through the appearance of blur, of any unsuspected fast component of motion. Stereo pairs can be laid down on successive frames by two adjacent roentgen-ray tubes that are alternately pulsed between frame scans.

To fully use the available band width, the amplifiers must carry a signal at all times. Slowing the camera from 30 frames per second to 24 can be done with feedback controlling the television frame rate as indicated above. If band width limits the image quality (it should not), then appearance will improve. Fifteen frames can be had without feedback by employing a 15 frame film speed and interlaceless raster at 30 frames with a full forward vertical sweep on the output tube while blocking both the detector and output tubes' scanning beams every other frame. Storage time is the same with or without interlace; besides implications for exposure and storage perfection, this means that alternate fields of a frame cannot separately be recorded to form a double speed film of half vertical resolution unless one broadens the detector spot vertically so all stored information is taken in each field. A 24 frame rate is for the recording of sound (time markers, commentary and body sounds) and its reproduction in teaching films shown on unaltered movie projectors. However, changes in frame rate by a factor of two can be had without change in pitch, or loss of intelligibility of accompanying sound, by the use of a periodic-sampling time compressor or expander.[1]

If detector storage is perfect (this does not blur motion as would increased phosphor persistence), then an unfiltered roentgen-ray voltage source will not degrade the image if there is an integral number of electrical cycles (or identical half cycles from a full wave circuit) in one frame time, because all points will "see" the same full cycles of roentgen-ray intensity before being sampled again. Slight banding of the image has been observed due to lack of perfect storage with an RCA 6849 image orthicon.

Across the picture on the viewing monitor appears a thin line that can be moved to cross the region of interest. On an adjacent oscilloscope appears the brightness pattern along this line; when this just fills the graticule, gain and brightness are adjusted so that the subject is optimumly matched to the full range of the film. (An exposure meter does not allow for range or important small structure.) For initial use, a graph of film density versus grid voltage is needed. A block diagram of the circuit is shown in Figure 4 and some observed patterns in Figure 5. With this method one can emphasize a particular structure in a systematic way, or alternatively, be sure of including all structures of interest.

Roentgen-ray intensity is separately set so that the *darkest* region of interest matches a predetermined intensity; structure there will then be statistically adequately defined, as it will be in all brighter regions. If finer detail is expected then this intensity is raised accordingly. To decrease the smallest resolvable distance by n means increasing the dose by n^2 since the number of quanta that formerly went through any unit area must now traverse each area smaller by n on a side.

MAGNETIC TAPE RECORDING

A magnetic video-tape recorder proves to have enough band width (4.5 megacycles) to replace the camera for many purposes if the image quality is always degraded by dose reduction to the minimum acceptable, as it should be. Such a unit records with a resolution of approximately 400 lines in the horizontal direction and 500 in the vertical direction, which is about as good as the information that our detector will supply at low light levels. The tape recorder shares the advantage of the shutterless camera in losing no interacting quantum, and it can be used as an erasable intermediate storage from which interesting material can be

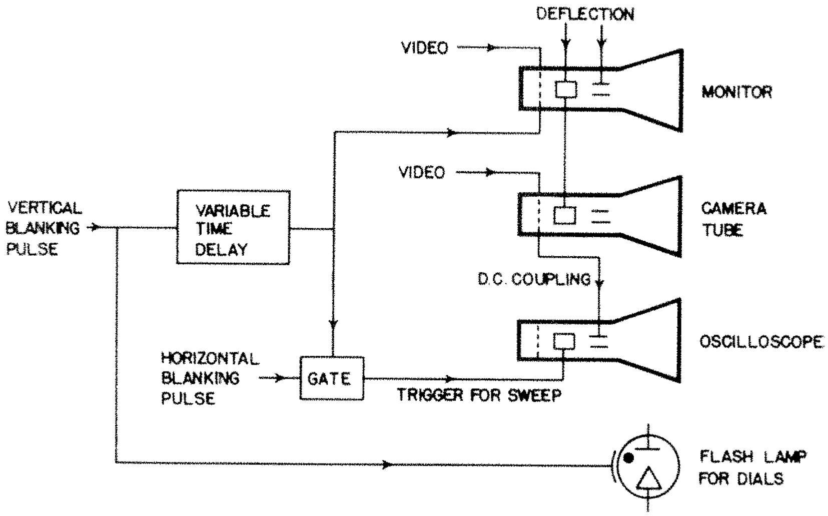

Fig. 4. Scheme of circuit used to systematize exposure control. The delayed sweep control on a Tektronix 545 oscilloscope will supply these functions.

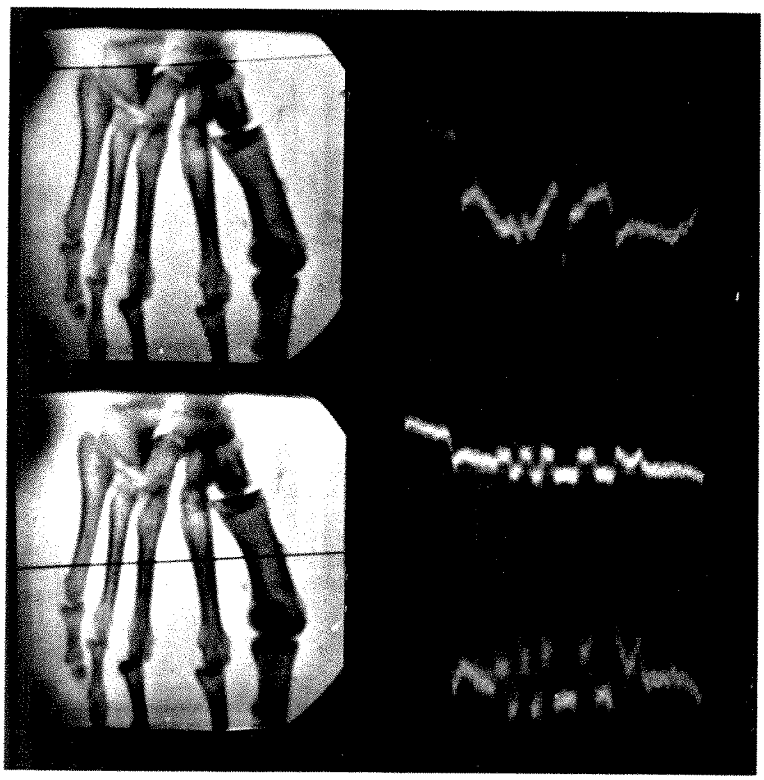

Fig. 5. Monitor displaying some hand bones, and the intensity pattern corresponding to a certain line of the image. When adjustment is such that the pattern falls within the two center lines of the graticule, then that portion of the image will be recorded properly. Portions of the image outside this voltage range will fall in the saturation regions of the film characteristic and will be ignored. The lower example shows two gain and bias settings, increasing darkness being upward.

transferred to film. The recorder gives a record that is immediately available for study, or redoing if some aspect of interest is not captured. Experience may show that in practice the greatest saving in dose will result from taking only as many frames as needed rather than exposing extra "precautionary" footage before releasing the patient.

With an image recorded in this form, image processing[2] can be optimized by varying parameters (*e.g.*, the amount of derivative mixed with an image to emphasize contours) while comparing the modified and unprocessed images on two monitors. One investigation will take two signal levels and from them, introduce color into the image by the Land method[3] to observe the effect on detail perception. (Minimum dose requires either monochromatic roentgen rays or a true color display, which the previous is not because of the mixing of the effect of the various roentgen-ray wave lengths.)

At present the following practical observations can be made in connection with tape recorders. It is extremely convenient that anything seen on the monitor is properly recorded, and the eventual appearance can be modified as desired during playback. Time, labor and extra equipment for film processing are dispensed with. The fast rewind feature in many cases allows almost the same result as the single-frame viewing possible with film, though single fields can be studied by using such a storage tube as the Tonotron. The appearance of the image is relatively satisfying and has proved useful clinically.

NOISE

The effect of a nonlinear system on the signal-to-noise ratio is difficult to predict and must include the signal distribution, the noise distribution and the position, extent and shape of the nonlinearity. However, when fluctuations in a brightness level are all small with respect to the magnitude of that level, as are most signals that would be enhanced, then contrast enhancing nonlinearities will not significantly change the signal-to-noise ratio. Thus after such enhancement, distractions from pattern are the same, but previously unnoticeable things are accessible to the visual system. Large noise pulses will diminish in relative effect after contrast enhancement if they are limited by a saturation nonlinearity while the smaller useful signal is expanded. Similarly, very contrasty structures may become no more important and thus they may be relatively less distracting. But it should be remembered that smooth test objects, such as partial holes in a metal plate, can give rise to overly optimistic views of the utility of such procedures because there are cases where recognition is not limited by contrast.

The signal-to-noise ratio is the same with a continuous or with a pulsed roentgen-ray source for a given dose. It should be noted that there is *not* adequate evidence that the biologic effects of the dose in the two cases is the same.

It is assumed that normal precautions are taken in the use of the detector. Thus, with an image orthicon the scanning beam must be no more intense than required to just discharge the highlights. Wallman has noted that high frequency noise is less disturbing to the recognition of pattern than low frequencies, and that a vidicon concentrates its noise at the higher frequencies while an image orthicon has a more uniform noise spectrum. Limiting the amplifier frequency response to just that required to carry the picture does not seem to help clarity much, probably because of the smaller importance of the fine parts of the noise pattern.

One comment on the size of the detector might be warranted. Increasing the diameter of an image orthicon used with a given speed lens is useful because, though there are no more "lux," there are more "lumens" (*i.e.*, the flux is increased but the illumination is not). Thus the total current will increase since a photocathode is characterized by a certain number of lumens per microampere. Fluctuations will tend to in-

crease with the square root of the current and thus the net advantage is a slowly increasing one as the area is increased.

A synchronous camera motor eases problems of hum, pickup, stray magnetic fields and power supply ripple, mainly because induced nonuniformities then tend to be stationary with respect to the image.

The disturbing scanning line structure in a television image, since it is periodic, can be eliminated in a photographic record by a suitable filter placed before the camera lens.[8] In the case of the continuous film movie camera, a slight vertical blurring of the scanning spot on the camera tube may be as effective.

SUMMARY

A television link with nonlinear circuits aids roentgen-ray movie production in allowing concentration on a small brightness range and also dose can be determined by the detail to be observed rather than by film properties. A continuously moving film camera viewing a single line on the kinescope, or a video magnetic tape recorder, need lose the effect of no interacting quantum. The frame rate aspect is considered and a systematic exposure procedure is given. A roentgen-ray beam energy monitor is also described.

The probable course of certain future developments is given as well as suggestions for the best use of existing detectors.

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The camera was constructed by Alan Cline, and John Kafafian investigated many of the circuit details. Dr. Earl Miller originated the recording of sound in this connection and also contributed to many stimulating discussions. Thanks are to be expressed to the Ampex Corporation for their loan of a video-tape recorder.

APPENDIX I

In connection with the evaluation of a roentgen-ray image in the form of a roentgenogram, it is convenient to have some measure of the possible information content of a film. The usual unit in information theory discussions is the bit.

One might estimate the number of bits of information in a standard 14×17 inch roentgenogram as follows. Suppose that each square millimeter can be significant, *i.e.*, there is no detail finer than this, but two such adjacent areas can be significantly different. And suppose each such area can have any one of a hundred distinguishably different densities. (For some applications this is a little unrealistic since one does not usually scan a film with a phototube and specify the absolute level at each point, except during television; the use of one's eyes is to distinguish any difference in intensity between two areas if it is more than roughly 1 per cent.) This implies approximately seven bits of information at each "point" since one would have to answer seven yes-or-no questions to state which of the 100 possibilities existed, *i.e.*, there are seven places of 0 or 1 in the binary number representation of 127, and six figures would only cover through 63 possibilities. The number of bits N at each region is:

$$2^N = 100 \quad \text{so} \quad 6 < N < 7.$$

Thus, the number of bits on such a film is roughly seven times the area in square millimeters, which is approximately a million.

Such a film could carry more than this by using its resolving power and exposure range to the maximum. The smaller films that are often used usually contain less information, but not necessarily less in proportion to their smaller area. This is because the finest recorded detail is usually smaller on such films. The information content of a small film would be as high as a large one if the small one were formed by clearly imaging a 14×17 inch fluorescent screen onto a small film of such resolving power that each unit area of the screen was still distinguishable.

The band width to transmit the above image at a 30 frame per second rate can be estimated by noting that a million choices between two voltage levels (*e.g.*, telegraph

key clicks) must be communicated in each 1/30 second interval. This will require a band width in cycles per second of approximately 30 million. This calculation implies the use of a binary code for transmission. Such a procedure is advantageous in the sense that noise will be less troublesome than if the signal level, from the hundred possible at each point, were sent directly, since the receiver need only be able to distinguish which of two levels exists at any instant. This signal sent in the usual way would require roughly a 5 megacycle band width. The source or nature of the noise must enter any detailed calculation of the band width required for the transmission of an image. A large roentgenogram can contain more detail than the above and require large band widths for faithful transmission if its quality is not attenuated by quantum fluctuations, screen noise, focal spot size, etc.

APPENDIX II

Present technology makes it conceivable that one can produce movies using spectral data to discriminate minute amounts of selected materials, and to enhance contrast generally over that found after ordinary roentgenographic processes that use lumped absorption information from many wave lengths. A scanning heterochromatic roentgen-ray beam would be used in conjunction with a very fast scintillation detector and pulse height analyzer (helped by delay-line pulse clipping) to record selected wavelength ranges in the emerging beam, rather than generating only a few discrete wave lengths, separated in time, as in the previous demonstrations.[2] For speed, it seems indicated that the equations giving the amount of the selected material[4] be solved by a simple analogue computer rather than being satisfied by the motion of wedges.

For example, if it is assumed that the qualitative analysis of the subject is two materials (soft tissue and iodine in the previous cases), then the two equations in terms of the four absorption coefficients of the two materials for the two wave length ranges, and the two intensity fractions k transmitted, are, for amounts of material t_1 and t_2:

$$\mu_{11}t_1+\mu_{12}t_2=\log k_1$$
$$\mu_{21}t_1+\mu_{22}t_2=\log k_2.$$

If material *one* is of interest then film blackening would be made proportional to:

$$t_1=\frac{\mu_{22}\log k_1-\mu_{12}\log k_2}{\mu_{11}\mu_{22}-\mu_{21}\mu_{12}}.$$

The denominator is constant in any one experiment.

In the previous method this signal would cause a compensating motion of a wedge of material *one*. In the present case, instead of wedges of the two materials being inserted in the apparatus, the corresponding μ's would be put in electrically. These can be determined from the original equations by noting the intensities transmitted at the two wave lengths by a unity density sample of material *one* when t_2 is zero, and vice versa. The main objection against not using wedges is that the variable number of emerging quanta per unit area indicates the application to the subject of some excess dose.[4]

In this method one quantitates the "hardening" of a beam as it traverses the subject. Rather than scanning with a special roentgen-ray tube like that of Moon, a lead Nipkow disk could be placed between the tube and the subject; a second one beyond the subject and moving synchronously with the first could help reject quanta that had scattered from the shorter wave length band into the longer. The use of ordinary filters and cycling Ross combinations is indicated to reduce the number of quanta from an ordinary tube that are in a useless wave length range, both for reasons of dose and also required detector speed. Special tubes in which there is composition modulation by an electron beam being shifted over a junction between target materials or by a roentgen-ray beam shifted over secondary emitters seem at present unduly complicated, though they would be

fast and feedback could maintain constant intensity. Methods related to the nondispersive infrared analyzers of the "negative-filter" type are also conceivable but more complex because roentgen-ray absorption spectra are not in the form of isolated lines or bands as in the infrared.

As an example of new results to be expected, calculation indicates that one can visualize inflammations by their more rapid uptake of large molecules[5] if these are iodine-labelled at a place where break-up will not too rapidly release the iodine to the thyroid. The same should be true of certain tumors which have a richer blood supply. It is here assumed that the finite energy resolving power of the detector does not impose a major extra limitation over the previous system using a special source, in which there are also technical performance limitations.

APPENDIX III

In graphs of the response of a system, sometimes linear and sometimes logarithmic coordinates are used. It is convenient to know the corresponding criteria for an increase in contrast in the two instances. It has been shown[2] that with linear coordinates there is an increase in contrast when the slope at the point in question on the graph of output intensity as a function of input intensity is greater than the slope of the line drawn from the point to the origin, that is, that dO/dI divided by O/I is greater than unity. On a logarithmic scale the slope is $d(\log O)/d(\log I)$. But:

$$d(\log O) = \frac{1}{O}\, dO \log_{10} e$$

$$d(\log I) = \frac{1}{I}\, dI \log_{10} e$$

or

$$\frac{d(\log O)}{d(\log I)} = \frac{dO}{dI} \Big/ \frac{O}{I}.$$

Thus with logarithmic coordinates, contrast will be enhanced at a brightness level that corresponds to a place on the curve where the slope is greater than unity. The photographic case is most familiar in which the maximum slope of film response is called gamma, and values greater than unity indicate increase in contrast.

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MEDICAL APPLICATIONS OF X-RAY TELEVISION

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SINCE the first medical application of the roentgen rays, continuous progress has been made both in the diagnostic and therapeutic domains in eliminating radiation hazards to which radiologists and operators of x-ray apparatus are exposed. Such fundamental means of protection as limiting the roentgen-ray beam by utilization of a multishutter and shielding the operator by walls of lead have proved of unquestionable value. The recent introduction of the image intensifier made possible remarkable further reduction in the exposure dose to the patient and the radiologist, and, at the same time, an improvement of detail perceptibility in fluoroscopy, but it still remained necessary for the radiologist to continue his studies in the fluoroscopic room, wearing a lead apron for protection. Why? The most important reason is that there has been no suitable optical device by which images on the photocathode screen of an image intensifier could be observed in another radiation-free room. In addition to this, it was rather difficult in practice to utilize the image intensifier alone in the fluoroscopic examination since its visual field was limited to a 5 inch circle. For this reason, an image intensifier and a routine fluoroscopic screen had to be used alternately or otherwise the image intensifier had to be moved in succession over several regions of the patient to perform a comprehensive examination. If a 9 or 11 inch image intensifier were utilized, the patient dose, as well as the scattered radiation dose to the radiologist during cineroentgenography or direct roentgenography on a tilting table, could likewise not be reduced substantially unless the television principle were applied. During the last few years, several reports concerning x-ray television have been published in Europe, the United States and Canada.[3–5] Since 1956, when the first attempt to utilize television in fluoroscopy was made by Nagaoka—one of the authors of the present paper—considerable research has also been carried out in Japan. In June, 1958, at the time that the construction plan of the Center for Adult Diseases—Osaka—was submitted, the authors projected the installation of an x-ray television system for practical use. Since August, 1959, when the closed circuit television for roentgen diagnosis in the Department of Radiology in the Center was installed, the basic and clinical examinations have been performed by this means. The purpose of the present paper is to report on the capability of the x-ray television unit, the first of its kind for practical use in Japan, and to discuss its possible applications.

EQUIPMENT AND METHOD

Description of the X-ray Television Device. As shown in Figures 1, 2 and 3, our x-ray television system consists of a high tension generator with a controller (maximum output: 50 ma. at 125 kv. or 500 ma. at 90 kv. for one second; and 3 ma. at 120 kv. for continuous use),* a Philips Symmetrix 90/90 tilting table with a rotating anode tube of 1×1 mm. focus, a Philips 5 inch image intensifier and a closed circuit television with a 14 inch and a 17 inch screen of the ordinary television picture tube for fluoroscopy and indirect roentgenography. In addition, a television camera and monitor for general viewing of a patient and a

* Manufactured by Shimazu Seisakusho Co., Ltd.

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† The Department of Electronics, Central Research Laboratories, Matsushita Electric Industrial Co., Ltd., Kadomacho, Osaka, Japan.

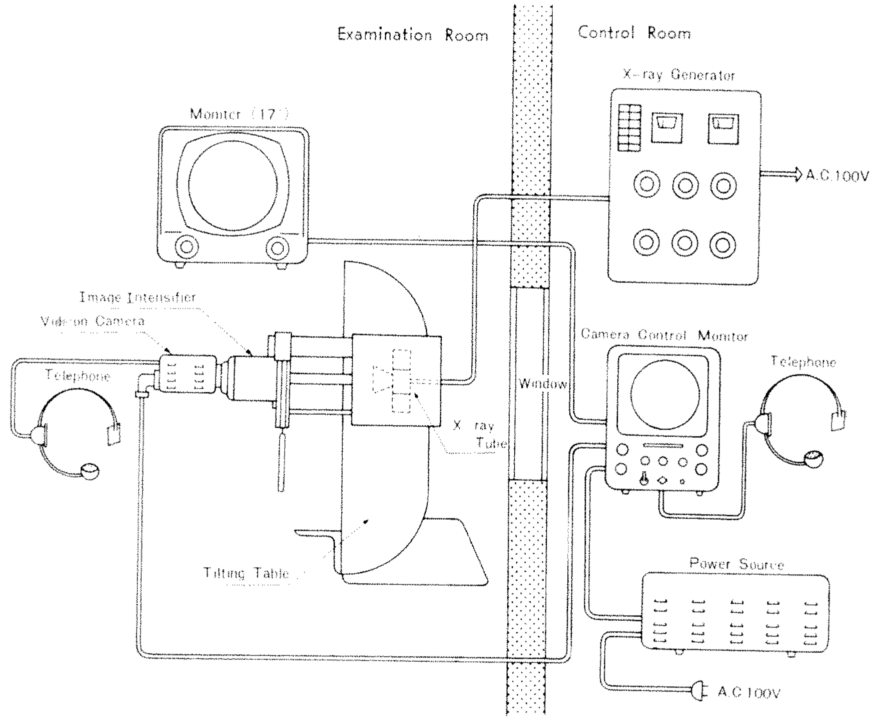

FIG. 1. General arrangement of the x-ray television equipment.

tilting table are provided.† Figures 3 and 4 show the television system in use.

Fluoroscopy. Radiologists can simultaneously view the fluoroscopic image through the television monitor screens, both in the control room (Fig. 3) and in the examination room (Fig. 4). Many physicians can take part in the fluoroscopic study with discussions by inter-telephones in brightly lit rooms.

•*Roentgenography.* Two different methods of roentgenography are possible with the television system: direct roentgenography on the tilting table and indirect fluororoentgenography through the television monitor. In the latter, the roentgen images on the 14 inch monitor in the control room are photographed either on 35 mm. roll films or by using 16 mm. cinefilms.

Detail Perceptibility. Seven groups of copper wires of different diameters (0.23, 0.25, 0.33, 0.4, 0.5, 0.6 and 0.7 mm.) are provided as a test chart for the examination of detail perceptibility. Each group consists of wires of equal diameter arranged on an extremely thin plate of plexiglass with the distances between them being equal to their diameters.

† The television system equipment is manufactured by the Matsushita Electric Industrial Co., Ltd.

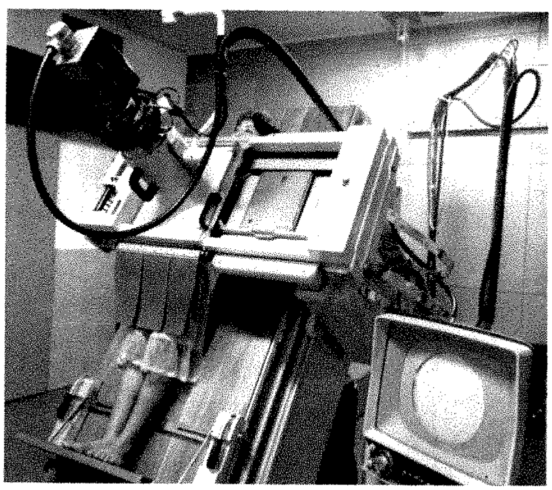

FIG. 2. Combination of Symmetrix 90/90 tilting table, 5 inch image intensifier and a closed circuit vidicon television camera with a 17 inch screen of an ordinary television picture tube for fluoroscopy.

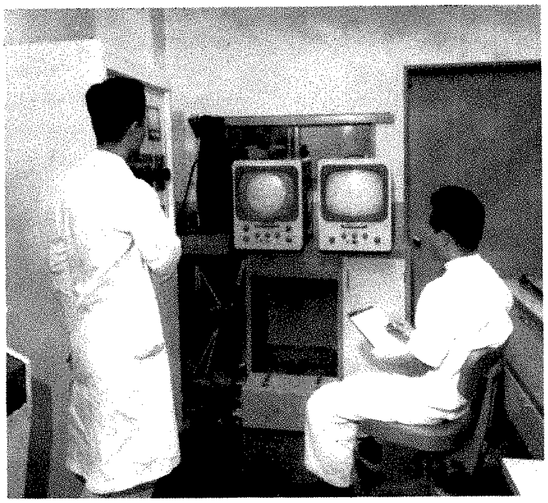

Fig. 3. The control room of the x-ray television system. There are two television monitors; the left one is for telefluoroscopy, teleroentgenography and telecineroentgenography and the right one for a general view of the examination room.

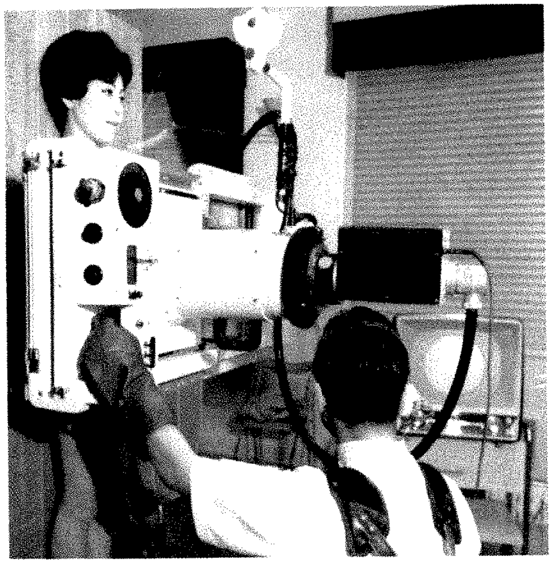

Fig. 4. The examination room of the x-ray television system.

Dose Meter. A Philips universal dose meter, type 37470, is employed. Ten plates of plexiglass, $30\times30\times1$ cm. in size, and a plate of plexiglass, $30\times30\times5$ cm. in size, are used as a phantom. These plexiglass plates can be added or reduced in number as the occasion demands.

Illumination Measurement on the Vidicon Faceplate. The direct measurement of illumination on the vidicon tube faceplate is difficult. Therefore, the luminous flux density at a fixed distance from the observation screen of an image intensifier is first measured by the use of a conventional illumination photometer. Secondly, by reproducing the same condition on an optical test bench, the illumination on the vidicon faceplate can be indirectly measured by the substitution method.

EXPERIMENTS AND RESULTS

TEST OF DETAIL PERCEPTIBILITY

A measurement of the detail perceptibility was performed using the copper wires with the smallest diameter of a group in which each of the wires was separately distinguished (Fig. 5, *A* and *B*). The detail perceptibility was evaluated with respect to: (1) fluoroscopy with the x-ray television monitor; (2) fluoroscopy with the image intensifier; and (3) fluoroscopy with the conventional fluorescent screen (Lerey-West "Sirius" HS screen).

The experimental data are shown in Figure 6; the distance of the focus to the photocathode screen of the image intensifier or of the focus to the conventional fluorescent screen was a constant 91 cm. The test chart was placed at a point 9 cm. from the photocathode screen of the image intensifier in the direction of the roentgen-ray tube when no phantom was used. With the phantom, the distance between the surface of the phantom facing the roentgen-ray tube and the focus of the roentgen-ray tube was always 58 cm. In the latter case, the detail perceptibility was evaluated by changing the depth of the test chart in a phantom 15 cm. thick; no detectable effect on the detail perceptibility was observed. Figure 6 shows that the detail perceptibility of the image intensifier is best, the x-ray television is slightly inferior to the former, and the conventional fluorescent screen is the poorest. As regards the detail perceptibility of the x-ray television system, one must take into consideration the fact that there is a significant difference due to the inclination of

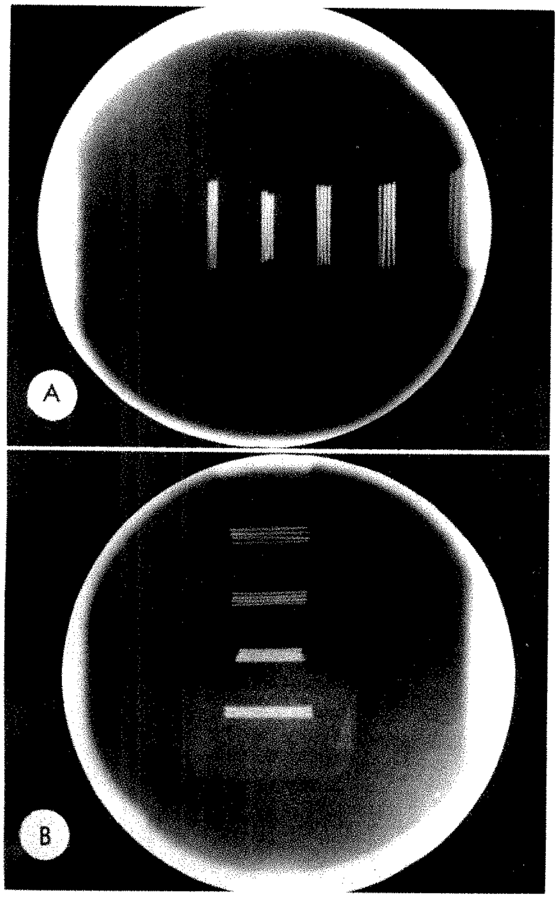

Fig. 5. Copper wires for the test of detail perceptibility. (*A*) The wires at right angles to the scanning lines of the television monitor are 0.4, 0.5, 0.6 and 0.7 mm. in diameter, left to right. (*B*) The wires parallel to the scanning lines are 0.7, 0.6, 0.5 and 0.4 mm. in diameter, top to bottom.

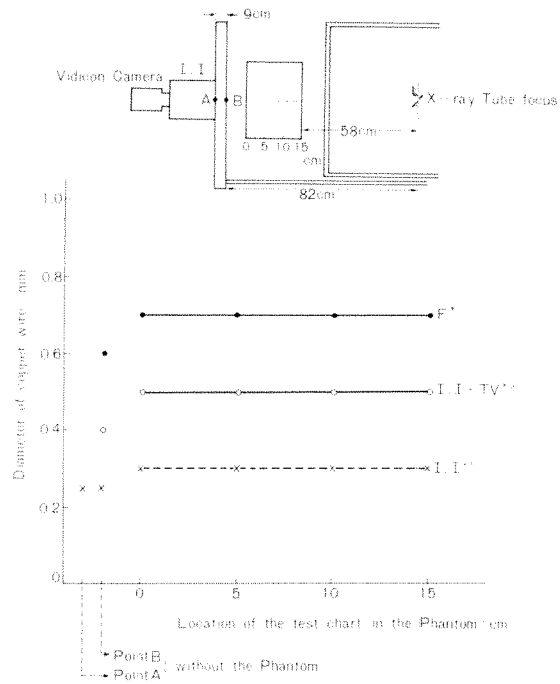

Fig. 6. Comparison of detail perceptibility of the fluoroscopic images by means of the conventional fluorescent screen, a combination of image intensifier and television, and image intensifier only.

Range of the diameters of the copper wires utilized for the test chart, 0.23–1.0 mm.; range of kilovoltage, 60–90 kv. peak; range of current, 2–3 ma.; focus size of the roentgen-ray tube, 1.0×1.0 mm.; grid ratio, 60–65/inch-24/cm.

*1 Conventional fluorescent screen.

*2 Combination of image intensifier and television.

*3 Image intensifier.

the copper wires of the test chart toward the scanning lines on the television monitor. When the wires are parallel with the scanning lines, the detail perceptibility is inferior by 0.1 mm. in diameter as compared to the case when the wires are vertical to the scanning lines (Table I and Fig. 5, *A* and *B*).

DOSIMETRY

The incident dose upon the object (*e.g.*, patient or phantom), the dose passing through the object and the scattered dose received during an examination were measured. The measurements were carried out by using the following factors: a 5 inch square roentgen-ray beam on the fluorescent screen, several kv. steps in the range from 60 to 120 kv., and currents of 2 and 3 ma.

Measurements of the Dose in the Plexiglass Phantom. The values of the incident dose upon a plexiglass phantom 15 cm. thick and the dose passing through it are given in Table II. That a relationship between the ratio of the exit dose to the entrance dose and the change of kilovoltage exists is evident (Fig. 7). Whether the x-ray television, the image intensifier or the conventional fluorescent screen is used, we can estimate roughly the patient dose received during fluoroscopy from this table. It was found that clear visualization of the pulmo-

TABLE I

COMPARISON OF JANKER'S AND THE PRESENT AUTHORS' DATA AS TO DETAIL PERCEPTIBILITY OF X-RAY TELEVISION SYSTEMS

Authors	Thickness of Phantoms (cm.)	Distance between the Test Chart and the Fluorescent Screen (cm.)	Minimum Diameter of Metal Wires That Are Distinguishable from Each Other (mm.)			
			F*	I. I.*	F+TV†	I. I.+TV*
Janker	0	0	0.4	0.3	0.8	0.6
Matsuda, Nagaoka, Takai, and Ninomiya	0	9	0.6	0.25	—	0.4 (0.5‡)
Janker	8		0.8	0.35	0.8–1.0	0.6
Matsuda, Nagaoka, Takai, and Ninomiya	15	9–24	0.7	0.33	—	0.5 (0.6‡)

* See Figure 6. F=conventional fluorescent screen; I.I.=image intensifier; TV=television.
† Combination of conventional fluorescent screen and television.
‡ Values in parentheses represent the detail perceptibility when the wires are parallel with the scanning lines of the television monitor.

nary field or the digestive tract with x-ray television was best accomplished by employing a current of 2–3 ma., and 70–75 kv. for the lungs (posteroanterior view), 75–80 kv. for the esophagus (oblique view), and 80–100 kv. for the intra-abdominal organs such as the stomach, the duodenum, the small and large intestines and the gallbladder. When the chest or the abdomen of a patient was thicker than usual, increase in the voltage did not show any appreciable improvement in detail perceptibility on the television monitor. From these clinical experiences and the experimental data, it seems to us that the necessary and satisfactory values in the ratio of the exit dose to the entrance dose are as follows: 0.7–1.0 per cent for fluoroscopy of the chest and 1.0–2.0 per cent for the abdominal organs (Table II and Fig. 7).

Measurement of the Patient Dose. We chose patients at random and measured the distribution of the dose in television fluoroscopy of the chest and abdomen with 2 ma., in relation to the thickness of the patient's

TABLE II

VALUES OF THE INCIDENT DOSE UPON A PLEXIGLASS PHANTOM 15 CM. THICK AND THE DOSE PASSING THROUGH THE PHANTOM USING A CURRENT OF 3 MA. THE ROENTGEN-RAY BEAM ON THE FLUORESCENT SCREEN WAS 5 INCHES SQUARE

kv.	Entrance Dose (r/min.)	Exit Dose (mr/min.)	Exit Dose / Entrance Dose (per cent)
60	1.57	14	0.82
70	2.36	28	1.10
80	3.15	48	1.52
90	3.88	75	1.93
100	4.66	100	2.14
110	5.32	125	2.34
120	5.50	148	2.69

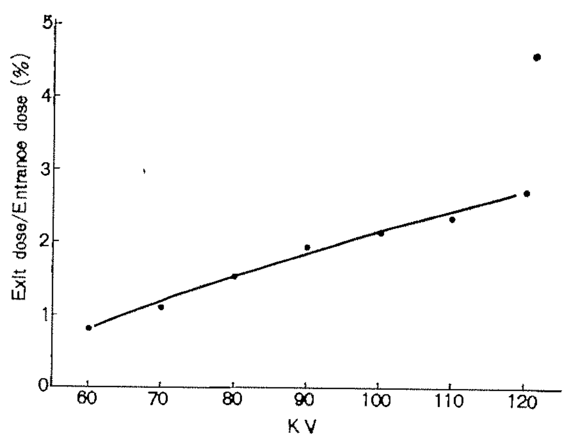

FIG. 7. Relationship between the ratio of the exit dose to the entrance dose and the change of kilovoltage using a current of 3 ma.

body (Fig. 8). The mean values were 2.0 ±0.3 r/min. for the chest and 3.4 ±0.7 r/min. for the abdomen. As may be seen from Figure 8, the thickness of the chest has no appreciable effect on the patient dose in fluoroscopsy of the lungs using television, although the dose increases gradually with the thickness of the abdomen in television fluoroscopy of the alimentary tract.

Measurement of the Scattered Ray Dose. The scattered ray dose of television fluoroscopy was measured perpendicular to the roentgen-ray beam at a point 100 cm. from the center of the phantom (Fig. 9), using 3 ma. and a 5 inch square roentgen-ray beam at the fluorescent screen. The amount of scattered radiation increases with increasing kilovoltage and the rate of increase is nearly linear up to 110 kv. As shown in Figure 9, at a distance of 100 cm. from the center of the patient, perpendicular to the direction of the roentgen-ray beam, the scattered dose will be approximately 0.15–0.2 mr/min. for examination of the chest, and 0.2–0.4 mr/min. for examination of the abdomen.

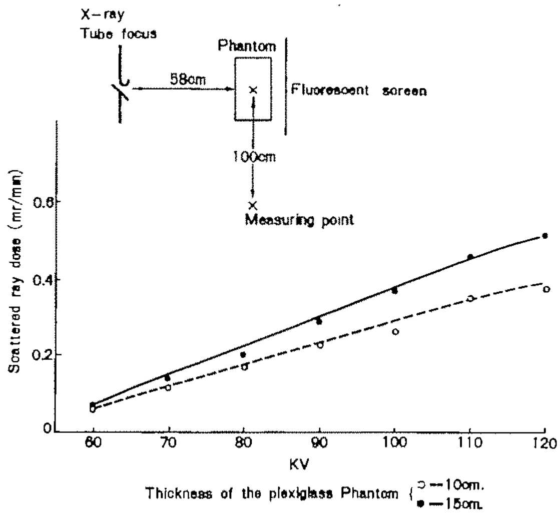

FIG. 9. Change of the scattered ray dose with change in kilovoltage using 3 ma. and a 5 inch square roentgen-ray beam on the fluorescent screen.

THE VIDICON FACEPLATE

The selection of the type of pickup tubes used for the television camera and also the design of the head amplifier depend upon the degree of illumination produced on the vidicon faceplate by the roentgen-ray image focused through a proper optical system from the observation screen of the image intensifier. Figure 10 shows the result of our measurements, using the substitution method. As may be noted, the relation of the respective changes between the illumination on the vidicon faceplate and the thickness of a plexiglass phantom, with 3 ma. and various kilovoltages applied to the roentgen-ray tube, can be expressed in an exponential function. A plexiglass phantom with a thickness of more than 10 cm. must be considered extremely unfavorable as regards the sensitivity of the vidicon type television pickup tubes.

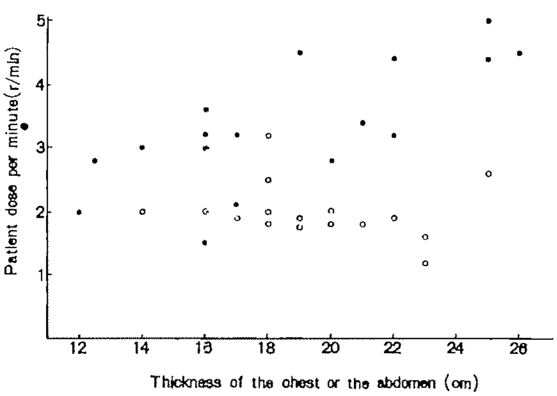

FIG. 8. Sharp contrast between the distribution of the patient dose in telefluoroscopy of a pulmonary field and that of an abdomen in relation to the change of the thickness of the patient's body.
○—Patient dose in telefluoroscopy of the lungs.
●—Patient dose in telefluoroscopy of the alimentary tract and gallbladder.

TELEFLUOROSCOPY AND TELEROENTGENOGRAPHY USING THE X-RAY TELEVISION SYSTEM

One of the most interesting characteristics of the x-ray television is that the radiologists can freely carry out teleroentgenography by using the monitor under conditions of routine fluoroscopy, while they perform telefluoroscopy with the same monitor. The technical factors for teleroentgenography are as follows: f=2.8; 35 mm.

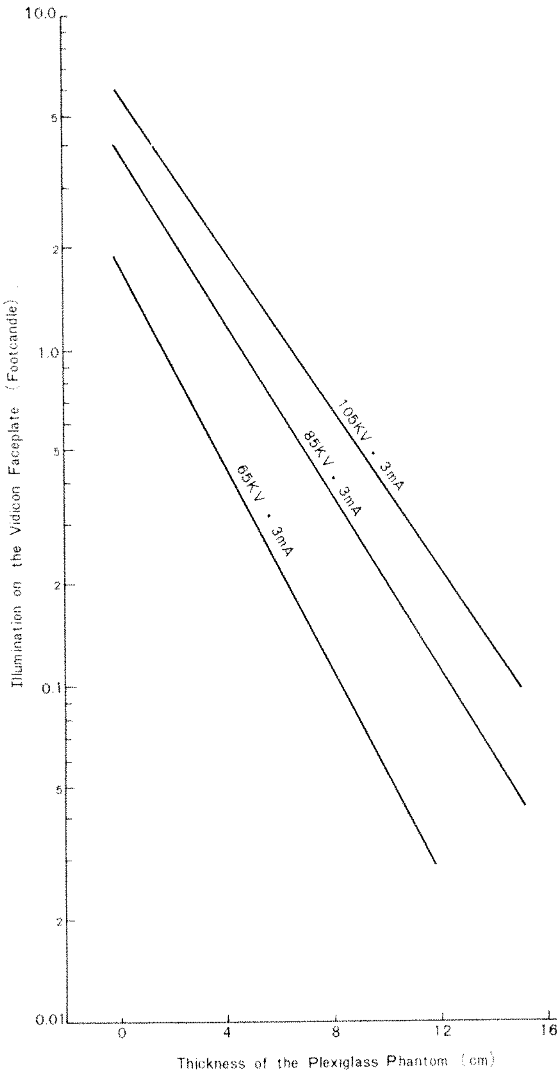

FIG. 10. Relation of the respective changes between the illumination on the vidicon faceplate and the thickness of a plexiglass phantom with 3 ma. and various kilovoltages.

Neo Pan SS, ASA 100 (Fuji) film; time of exposure = 1/10 sec.; distance = 3 feet, regardless of what part of the body is examined. Figures 11 to 13 illustrate indirect teleroentgenograms made by using the television monitor. It may be noted from these illustrations that the range of the x-ray television system is similar in teleroentgenography to that in telefluoroscopy, since both methods of examination are carried out under quite identical technical conditions and all regions of the body can be examined. However, it must be admitted that there is some difference in the ease of the examination depending on which part of the body is examined, as shown in Table III. This table was compiled from clinical experience with about 150 cases examined with x-ray television from October to November, 1959.

CINEROENTGENOGRAPHY USING THE X-RAY TELEVISION SYSTEM

Telecineroentgenography was performed by photographing the roentgen-ray images on the television monitor with a 16 mm. cinecamera (Arriflex) in the control room. The factors for telecineroentgenography were as follows: f = 5.6; Fugi x-ray film for fluorography; 15 frames/sec.; distance between the monitor and the cinecamera, 3 feet. Kilovoltage and milliamperage were the same as for telefluorography. Hence, the patient dose received during telecineroentgenography was equal to that received during telefluoroscopy, that is, 2–5 r/min. (Table IV). The regions examined by telecineroentgenography were the pulmonary fields, heart, aorta, trachea and bronchi after bronchography, the esophagus, small and large intestines after the ingestion of a barium meal, the sigmoid colon and large intestine after a barium enema, and the gallbladder after cholecystography using telepaque. Figure 14 shows clearly that telecineroentgenography using the x-ray television system is of definite diagnostic value in these regions.

DISCUSSION

Construction Problems. X-ray television units are roughly classified into two types depending on the kind of pickup tube employed. This is either the vidicon or the image orthicon. An example of the former is the Philips unit[1] and of the latter are Janker's[3] and Marconi's units. There are two fundamental reasons why we have adopted the vidicon camera system. The first is that the device with this system can be operated by radiologists without the

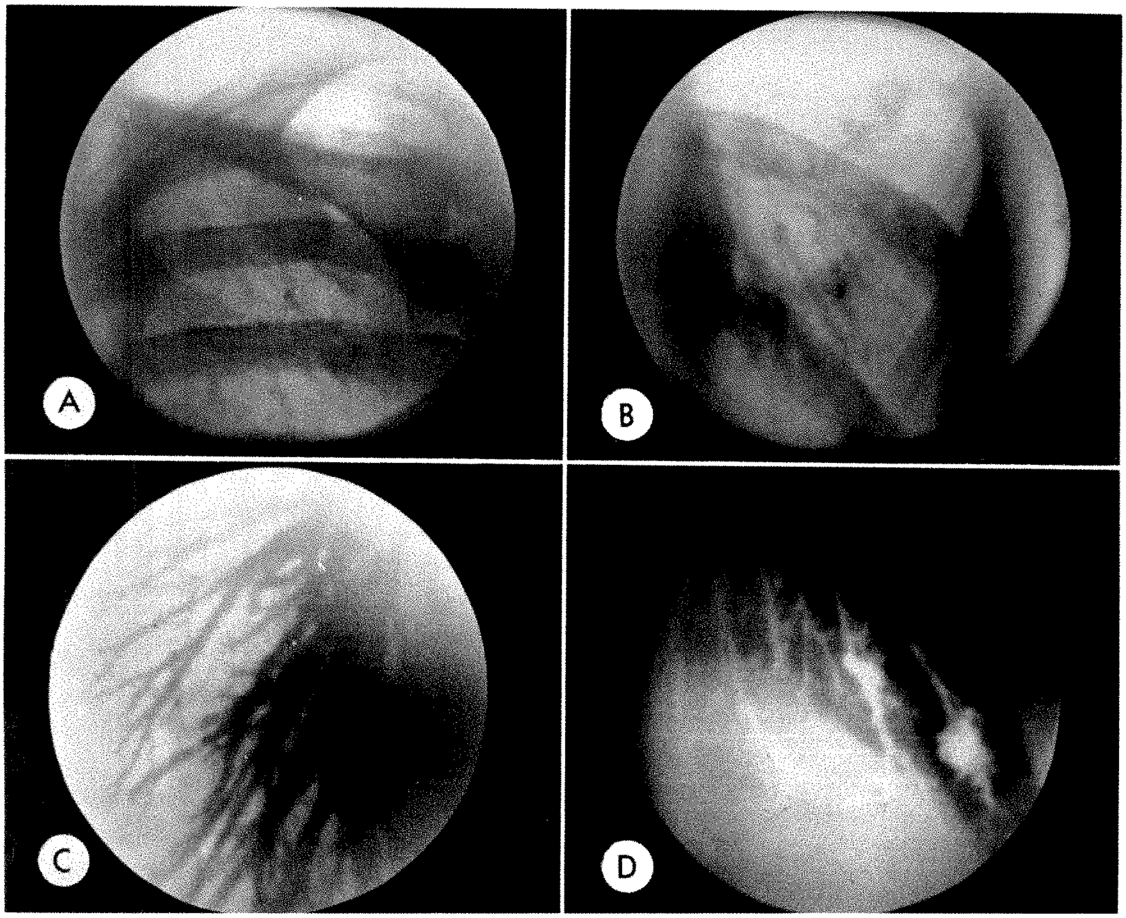

Fig. 11. Teleroentgenograms of the pulmonary field using the television monitor. (*A*) Upper region of the right lung field. (*B*) Lower region of the left lung field. (*C*) Normal bronchial tree. (*D*) Deformed bronchial arborization due to chronic bronchitis.

need of electronic engineers. Secondly, the signal to noise ratio of the televised roentgen-ray image is far better than that of the image orthicon camera. The image orthicon camera is, as is well known, extremely sensitive in comparison with the vidicon; therefore, it is capable of catching the image on the conventional fluorescent screen without the aid of the image intensifier, the use of which is indispensable to the vidicon camera. However, a comparison of Janker's[3] data with those of the authors' (Table I) shows that the combination of the image orthicon camera and the conventional fluorescent screen leads to conspicuous deterioration in detail perceptibility, while the vidicon-image intensifier system is by no means inferior to the image orthicon-image intensifier system in the detail perceptibility. Under the circumstances we undertook a study of the x-ray television system by means of the vidicon-image intensifier combination. The sensitivity of the vidicon camera was not always satisfactory in the last few years, so the image orthicon camera has been temporarily used. It is our impression that the range of the image orthicon camera, in the future, will prove useful in particular problems.

Perceptibility Problems. These deal primarily with the focus size of the employed roentgen-ray tube. We have used a roentgen-ray tube of 1.0 mm. focus in our experiments. However, we found that a smaller focus of 0.3 mm. in size will give

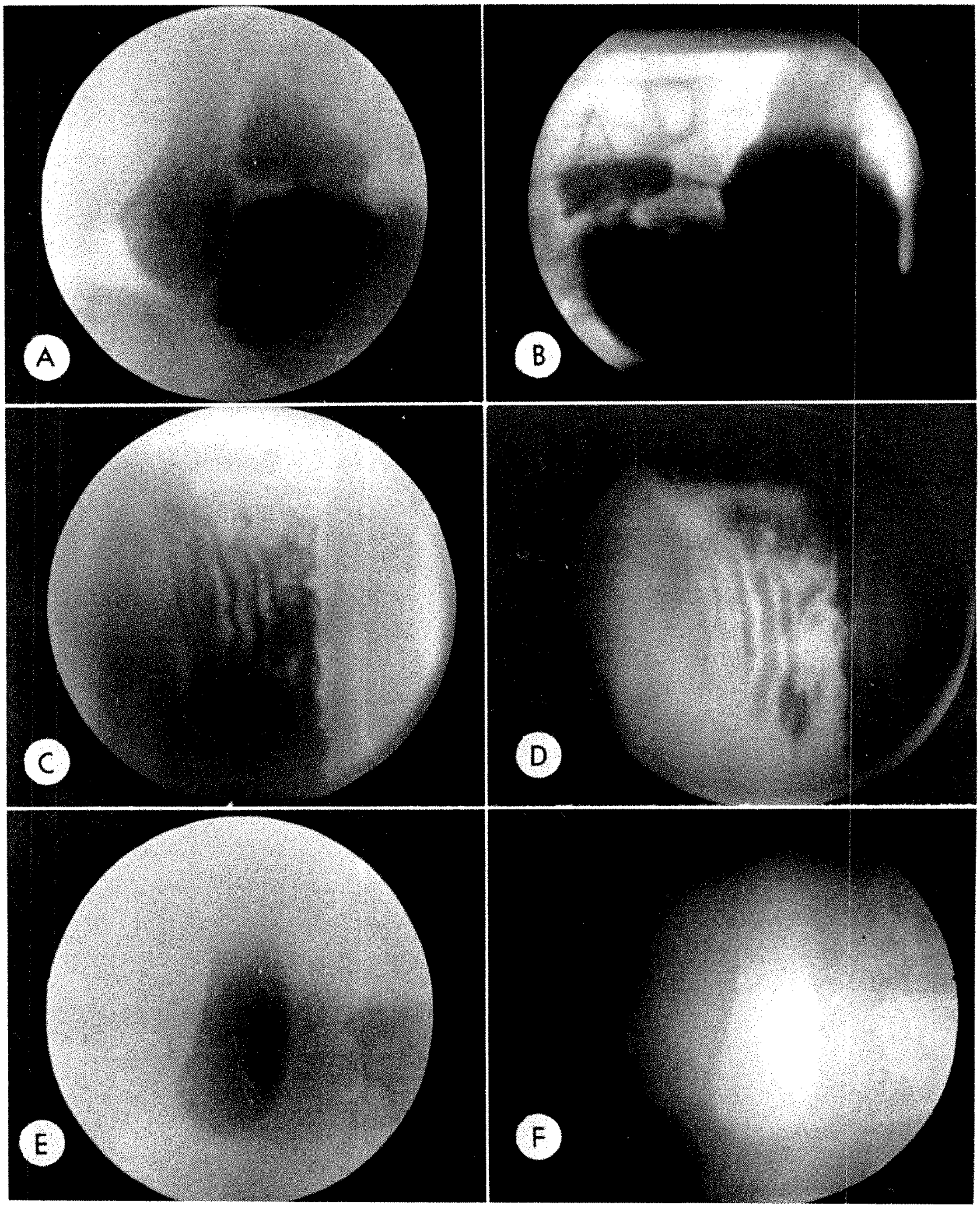

Fig. 12. Teleroentgenograms of the alimentary tract and gallbladder. (*A*) Prepyloric antrum, duodenal bulb and gallbladder. (*B*) Stomach and duodenal bulb. (*C*) Relief pattern of a stomach (positive view). (*D*) Relief pattern of a stomach (negative view). (*E*) Gallbladder (positive view). (*F*) Same gallbladder (negative view).

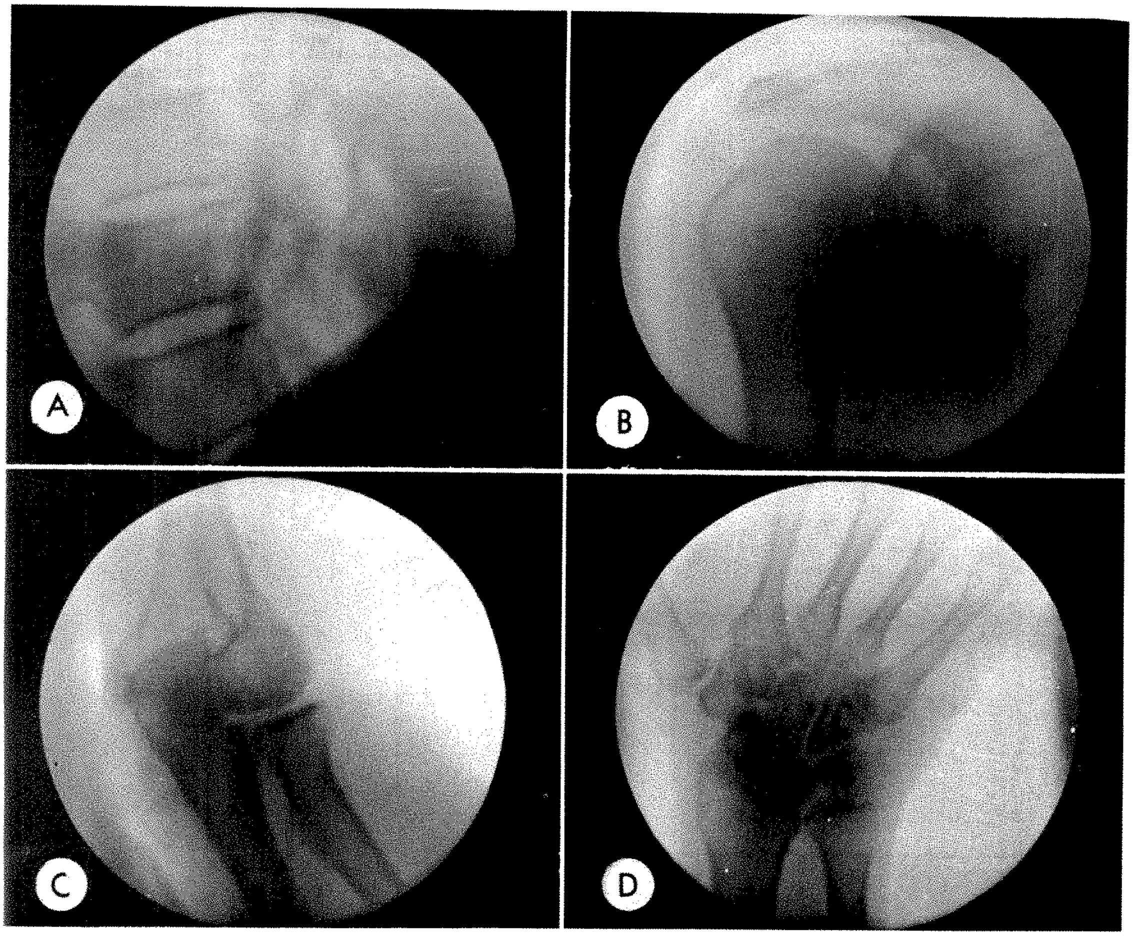

Fig. 13. Teleroentgenograms of bones. (*A*) Dorsal spine (lateral view). (*B*) Shoulder joint. (*C*) Elbow joint. (*D*) Wrist joint.

better detail perceptibility. Secondly, there is a slight difference in detail perceptibility depending on the direction of the object to the scanning lines of the television monitor (Table I and Fig. 5). With our present equipment, the difference in detail perceptibility is 0.1 mm. This is inherent to the 525 line square scanning system. We hope to adopt a 625 line system and thereby eliminate this difference.

Sensitivity Problems. Although our x-ray television system has a wide range of diagnostic possibilities in most regions of the body, it is, to an extent, limited. We were not able to get sufficiently clear images of the bony structures of the hip joint, head, upper dorsal spine and of the lateral view of the lumbar spine. Also, it was hardly possible to diagnose the lesions in the digestive tract of men who had an abdominal thickness above 25 cm. (Table III).

In order to overcome these difficulties, we feel that the following factors may prove helpful: (1) increase in milliamperage, (2) employment of a more sensitive vidicon tube in low brightness level, and (3) improvement in the efficiency of the optical component between the image intensifier and the vidicon camera. Usually, we employ a current of 2–3 ma.; however, we were able to get extremely clear images on the television monitor by temporarily increasing the milliamperage to 6 ma. without changing the kilovoltage (Fig. 12*B*). Our x-ray television unit is now under reconstruction with these points in mind.

TABLE III

CLASSIFICATION OF THE ORGANS OR REGIONS OF THE BODY ACCORDING TO THE EASE OF FLUOROSCOPY USING X-RAY TELEVISION

Ease of Fluoroscopy	Organs or Regions (nature of examination)	Direction of Roentgen-Ray Beam
Extremely easy	Lung	Posteroanterior, oblique
	Trachea and bronchi (bronchography)	Posteroanterior, oblique, lateral
	Heart and aorta	Posteroanterior, oblique
	Esophagus	Oblique
	Sigmoid colon and colon (barium enema)	Posteroanterior
	Cervical spine	Posteroanterior, lateral
	Middle and lower portions of a dosal spine (except D10 and D11)	Lateral
	Bones of extremities Shoulder joint Elbow joint Wrist joint Knee joint	Posteroanterior, oblique
	Bladder and urethra (cystourethrogram)	Posteroanterior, oblique
Easy*	Stomach Duodenum Small and large intestine (oral method) Gallbladder	Posteroanterior, oblique
	Lumbar spine	Posteroanterior
Rather difficult	Hip joint	Posteroanterior,
	Head	Posteroanterior, lateral
Difficult	Dorsal spine	Posteroanterior
	Upper dorsal vertebrae	Lateral
	Lower dorsal vertebrae (D10–D12)	Posteroanterior, lateral
	Lumbar spine	Lateral

* Clearness of fluoroscopic images as to these regions is influenced by the thickness of the abdomen. Hence, in general, the ease of telefluoroscopic diagnosis based on the thickness of the abdomen is as follows: under 20 cm. thick-easy, 20–24 cm. thick-moderately difficult, over 25 cm. thick-difficult.

In a future report, the experiences with the new unit and its diagnostic capability will be described. The timely introduction of the storage tube will make it possible to store electronically these extremely dis-stinct images for any length of time without further radiation to the patient.

Effective Visual Field. The size of the effective visual field in the x-ray television unit of the vidicon tube and image intensifier system is limited by the diameter of the image intensifier. We now use a 5 inch image intensifier; however, it will be replaced by an image intensifier of a larger

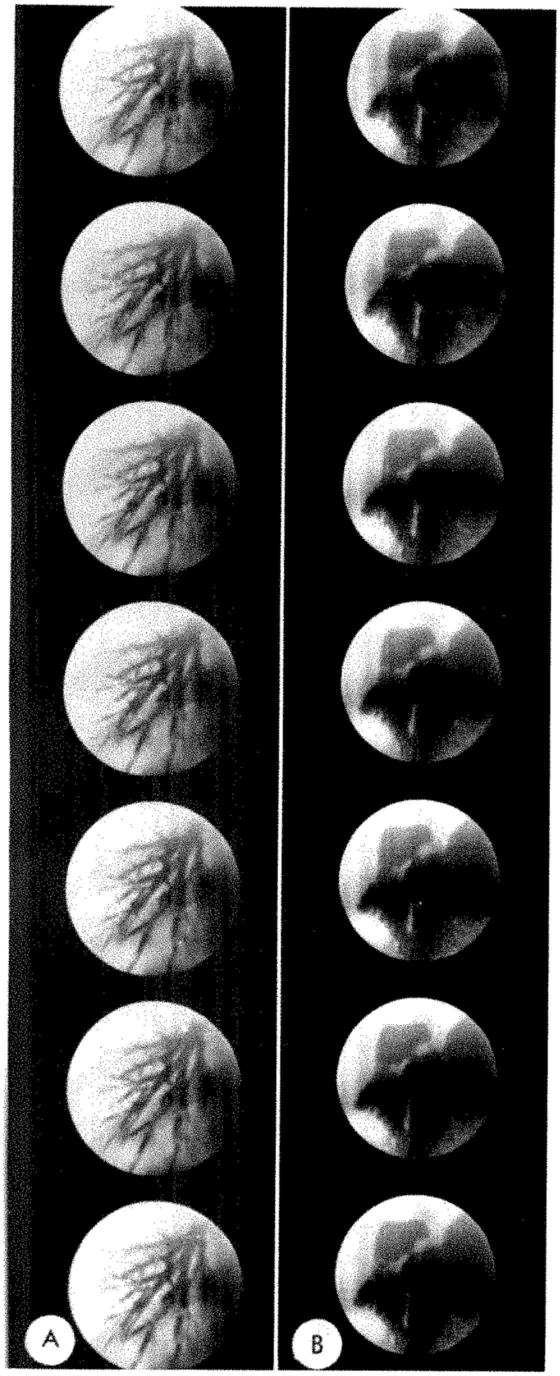

FIG. 14. (*A*) Telecineroentgenograms of a normal bronchial arborization, and (*B*) of the stomach and duodenum.

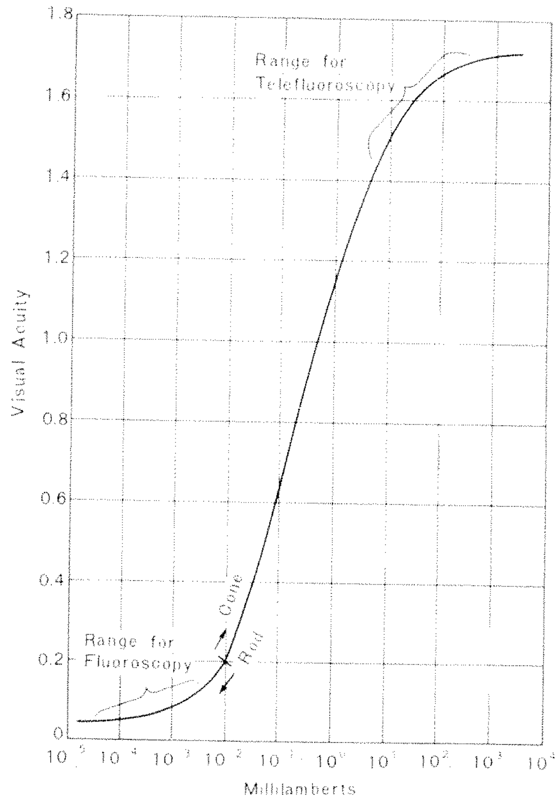

FIG. 15. Relationship of visual acuity to illumination; the brightness of the conventional fluorescent screen was in the order of 10^{-4}–10^{-3} millilamberts. Sharp vision is impossible at this low level brightness because observation takes place by means of the rods, localized at the peripheral parts of the retina, while with high brightness levels used in telefluoroscopy, observation is by the cones, situated at the central zone of the retina.

diameter. The 5 inch image intensifier is apt to be insufficient in clinical use and radiologists expend a great deal of work and time because of inevitable traveling of the visual field. Too, the necessary additional radiation exposure may bring about unfavorable effects. For these reasons an image intensifier of over 9 inches in diameter is recommended.

EVALUATION

Telefluoroscopy. Roentgen-ray images on the television monitor are very much superior to those on the conventional fluorescent screen in both brightness and sharpness. This means that the value of fluoroscopy—more exactly telefluoroscopy—is greatly increased in the domain of roentgen diagnosis. Hitherto, not only the inexperienced but also an experienced radi-

TABLE IV

RADIATION DOSE IN CONVENTIONAL CINEFLUOROGRAPHY AND IN TELECINEFLUOROGRAPHY

Method	Area	Authors	Kilo-voltage	Milli-amperage	Dose (r/min.)	Frames per sec.
Image Intensifier	Chest	Feddema	70	10	9	32
	Esophagus	Allcock and Barridge	95–120	6–17	13.5–42	16.6
	Stomach	Philips advertising	120	12	13	16
	Duodenum and small bowel	Feddema	120	11	20	16
Image Intensifier plus Orthicon	Chest and stomach	Janker	90	2–4	5–10	25
Image Intensifier plus Vidicon	Chest	Matsuda, Nagaoka, Takai and Ninomiya	65–70	2	1.5–2.5	15
	Esophagus		75–80	2	3	15
	Stomach, duodenum, and intestine		75–100	2	3–5	15

ologist would hesitate to make a positive diagnosis of diseases of the chest or digestive tract by fluoroscopy alone, without study of roentgenograms of those patients. Owing to the fact that there is 100,000 times as much brightness as on the conventional fluorescent screen (Fig. 15),[2] telefluoroscopy—fluoroscopy using the television monitor—is carried out by the cone-vision of the retina, while conventional fluoroscopy requires the rod-vision. This is probably the most important reason for the remarkable improvement of detail perceptibility in telefluoroscopy. When the detail perceptibility of the roentgen-ray shadow by means of telefluoroscopy becomes comparable to that of conventional roentgenography, it is possible that telefluoroscopy may replace direct roentgenography.

Indirect Roentgenography and Cineroentgenography. One of the greatest advantages of the x-ray television system is that the operator can freely take photographs of various organs of patients by means of a lens-shutter system camera or a cinecamera by using the x-ray television monitor during the course of fluoroscopy with complete protection against exposure to radiation. The authors again wish to emphasize that this type of indirect roentgenography, including telecineroentgenography, was performed with the same kilovoltage and milliamperage that they used in conventional fluoroscopy. This has an important bearing on the decrease of the patient dose in roentgen diagnosis. Telecineroentgenography—cineroentgenography using the x-ray television monitor—was performed at 15 frames per second because pictures are transmitted at 30 frames per second in our closed circuit television system.

Radiation Exposure of Patient and Radiologist. As regards radiation exposure, a line must be drawn between the dose received by the radiologist and that received by the patient. The radiologist and x-ray technician who are in the control room are completely protected against radiation throughout the course of fluoroscopy, roentgenography or cineroentgenography with the x-ray television monitor. However, since the tilting table which we now use is not remotely controlled, an operator is left in the examination room to select the visual field of the image intensifier, to roentgenograph directly and to tilt the table. We plan to remedy this by employing a fluoroscopic table operated by remote control.

The patient dose in telefluoroscopy, teleroentgenography and telecineroentgenography, regardless of whether the single or combined technique is used, is by no means greater than that in conventional fluoroscopy, but the relative patient dose in telefluoroscopy is greater than that in fluoroscopy using the image intensifier. For example, factors of 60 kv., 2 ma. for the chest and 75 kv., 2 ma. for the stomach and duodenum are adequate for obtaining clear images in fluoroscopy of patients who have a 20 cm. thickness of the chest and a 22 cm. thickness of the abdomen by using an image intensifier. In comparison, 75 kv., 2 ma. for the chest and 80 kv.–100 kv., 2 ma. for the abdomen are required in telefluoroscopy. Telecineroentgenography seems to have advantages over cinefluorography when the image intensifier is used (Table IV). In fact, cineroentgenography employing the x-ray television monitor appears to be one of the most useful techniques in the domain of roentgen diagnosis.

SUMMARY

The data concerning the construction and the diagnostic capability of an x-ray television system which is employed in clinical practice are presented. The advantages of this system to roentgen diagnostic procedures such as fluoroscopy, indirect roentgenography and cineroentgenography as well as the radiation exposure of the radiologist and the patient are discussed. Its contribution to definitive and efficient roentgen diagnosis is emphasized.

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DETAIL VISIBILITY IN RADIOGRAPHS: THEORETICAL STUDY OF THE EFFECT OF X-RAY ABSORPTION IN THE OBJECT ON THE EDGE SHARPNESS OF RADIOGRAPHIC IMAGES*

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IMAGE sharpness is one of the numerous variables which influence the visibility of small details in a radiograph. The impression of sharpness gained by an observer is due to his reaction to stimuli received by his eye when it scans across the edge of an image on the radiographic film. These stimuli are some function of the density distribution at the edge which, in turn, is caused by the physical interaction of the penetrating radiation with the object and the film. Thus it appears that the final impression of sharpness is the result of a "chain reaction" passing from initial physical factors through physiologic reactions to the final subjective judgment. In short, sharpness is a psychophysical quantity. The question arises: "What is the link between the physical phenomena and the subjective judgment, or what measurable quantity makes one density distribution appear sharp and another unsharp?" The answer to this question is important because the density distribution on the film may be influenced by improved radiographic materials and techniques. In preparation for the investigation of this problem, it is of value to study the relationship between the density distribution in the image and the interaction of the penetrating radiation with the object and the film.

Physical factors affecting edge sharpness in radiographic images have been discussed by many authors.[1,4–9] Apart from certain characteristics inherent in photographic emulsions, *e.g.*, graininess, turbidity and developer effects, which limit the edge sharpness attainable, the following principal factors are usually held responsible for the unsharpness of a radiographic image: (a) movement unsharpness—caused by independent movement of the object, film, or source of radiation; (b) geometric unsharpness—arising from the finite size of focal spot or source of radiation; and (c) screen unsharpness—primarily due to the scattering of light in the intensifying screen.

Movement, geometric and screen unsharpness, separately and in combination, have been investigated theoretically and experimentally. They are often expressed in terms of the distance, measured on the image of an edge, over which the density changes continuously.

It is not clear, however, that this measurable quantity relates in general to the subjective impression of unsharpness. In fact, it will be shown later that this quantity cannot take into account certain additional physical factors, because in practical cases it may be impossible to define the endpoints of the interval by the simple statement that they are the points at which the density begins or ceases to change continuously. Also, it has been established for photographic images that sharpness is a function of density gradient at the edge,[2] and that a discontinuous density change (infinite density gradient) at the edge would give the impression of perfect sharpness. There is no obvious reason why a similar relationship should not apply for radiographic images.

In all cases, the derivations were based on the assumption that the object forming the edge had negligible thickness *and* was totally absorbing. Although this approach is instructive as a first approximation, it is felt that the restrictions are somewhat severe and that the results are unneces-

* Communication No. 2087 from the Kodak Research Laboratories.

sarily far removed from the actual phenomena. In reality, radiographic objects are, of course, of finite thickness and usually absorb only part of the radiation. The amount absorbed is dependent on the distance traversed by the radiation inside the object (as well as on wavelength, atomic number and specific gravity). When this is taken into account, it is apparent that it is impossible in practice to obtain a discontinuous change of photographic density at the image edge even if geometric, motion and screen unsharpness are negligible. This can be demonstrated mathematically for the following special case which is of interest as a first approximation to practical problems arising in medical radiography.

Let parallel penetrating radiation be incident perpendicular to the axis of a cylindrical object with the linear absorption coefficient μ_2 immersed in a material having linear absorption coefficient μ_1, and let us assume that the radiation is monochromatic and that no scattering occurs in the substances (Fig. 1). This situation is quite unrealistic, but it serves to demonstrate the effect of absorption in the object without the introduction of complicating factors. In a later study, some of the restrictive assumptions will be removed and the results will be more nearly applicable to practical situations.

From Figure 1 it follows that

$$\left(\frac{y_2}{2}\right)^2 + (r - x)^2 = r^2, \qquad (1)$$

where x is a linear coordinate measured in the film plane perpendicular to the axis of the cylinder, with $x = 0$ at the edge of the cylinder and $y = 0$ at the film plane. Then, solving equation (1),

$$y_2 = 2(2rx - x^2)^{1/2} \qquad (2)$$

and from Figure 1

$$y_1 = y_{11} + y_{12} = d - y_2. \qquad (3)$$

Now, for monochromatic radiation, the intensity in the film plane is given by

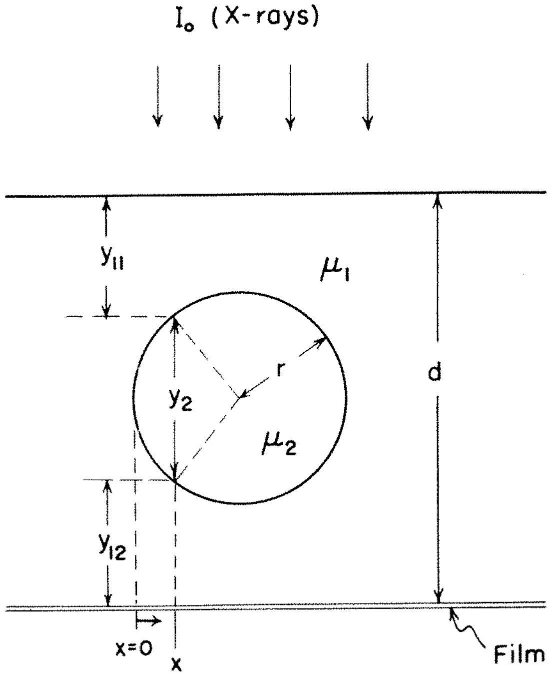

FIG. 1. Bone embedded in tissue (idealized).

$$I = I_0[\exp(-\mu_1 y_{11}) \exp(-\mu_2 y_2) \exp(-\mu_1 y_{12})]$$
$$= I_0 \exp[-(\mu_1 y_1 + \mu_2 y_2)],$$

so that from equations (2) and (3),

$$I = I_0 \exp - [\mu_1 d + 2(\mu_2 - \mu_1)(2rx - x^2)^{1/2}]. \qquad (4)$$

It is not sufficient to describe the resulting image in terms of radiation intensity in the film plane as given by equation (4). The response of the viewer's eye is some function of the film density and contrast which are related to the radiation intensity by way of the characteristic curve of the film. Thus the image characteristics depend on the type of film used and the exposure and development conditions, in short, on any phenomenon which affects the characteristic curve. This will be demonstrated, using as an example the characteristic curves of Kodak Blue Brand Medical X-ray Film and of Kodak No-Screen Medical X-ray Film, both for direct x-ray exposures.

We can write, in general, for the density

$$D = f(\log E) = f(\log It),$$

Table I

LINEAR X-RAY ABSORPTION COEFFICIENTS OF MATERIALS COMMON IN MEDICAL RADIOGRAPHY[8]

Material	Density (gm./cm.^{3})	Atomic No.	Mass Absorption Coefficient μ_p (cm.^{2}/gm.) 40 kv.	Linear Absorption Coefficient μ(1/cm.)
Tissue (water)	1.00	7.42	0.1046	0.1046 (μ_1)
Bone	1.85	13.8	0.0945	0.1748 (μ_2)
Air	0.0013	7.64	0.0943	0.00012 (μ_1)
Subcutaneous fat	0.91	5.92	0.0941	0.086 (μ_1)

where the functional relationship is given by the characteristic curve of the film. Then from (4) and the relation,

$$\log A = 0.434 \ln A,$$

we have, for the exposure on the film,

$$\log E = \log (I_0 t) - 0.434[\mu_1 d + 2(\mu_2 - \mu_1)(2rx - x^2)^{1/2}]. \quad (5)$$

In order to obtain a quantitative description of the density distribution on the film by using equation (5), let us choose an example from medical radiography. Consider the cylindrical object to be a thigh bone (here assumed to be homogeneous) embedded in tissue. Then, approximately, $r = 1.5$ cm., $d = 20$ cm., and from Table 1, $\mu_1 = 0.1046$ cm.$^{-1}$ and $\mu_2 = 0.1748$ cm.$^{-1}$. Equation (5) then becomes

$$\log E = \log (I_0 t) - [0.908 + 0.061(3x - x^2)^{1/2}]. \quad (6)$$

In conjunction with the proper characteristic curve of the film (Fig. 2), equation (6) yields values for the film density, $D = f(x)$, due to the x-ray exposure, $E = It$. The value of log $(I_0 t)$ may be chosen so that the theoretical density scale corresponds to the density scale often obtained in radiographs of this type. In order to facilitate comparison of the density distribution on the two types of film, we will select values for log $(I_0 t)$ such that the density in the image of the tissue alone is about 1.7 for both films. The minimum density at the center of the bone will then be a function of the absorption of the object and of the contrast of the film.

Figure 3 shows a plot of the film density as a function of distance measured from the edge of the bone image. It is seen that the absorption of x-rays in the substances causes a continuous change of density extending from the edge of the bone to the

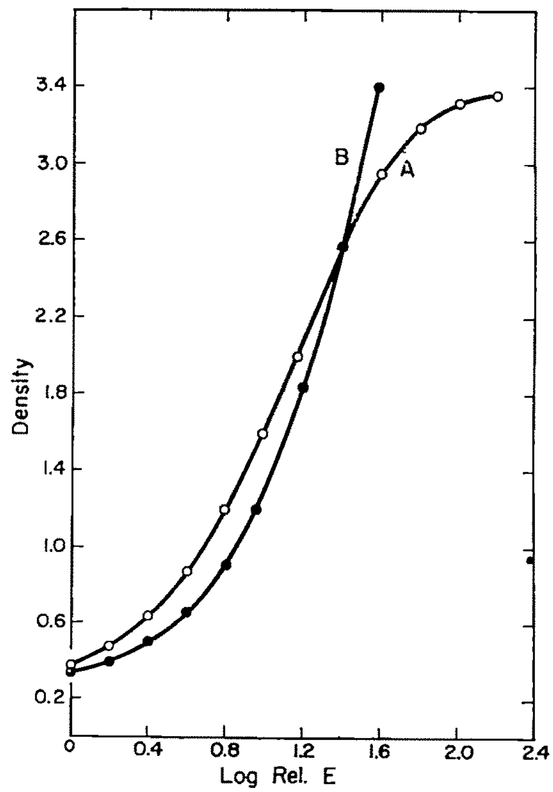

Fig. 2. Characteristic curves of Kodak x-ray films. (Reproduced from *Radiography in Modern Industry*, Supplement No. 2, Eastman Kodak Company, 1959, pp. 13 and 14.)

A—Blue Brand Film (direct x-rays). B—No-Screen Film (direct x-rays). (The two curves have been translated parallel to the abscissa in order to facilitate comparison.)

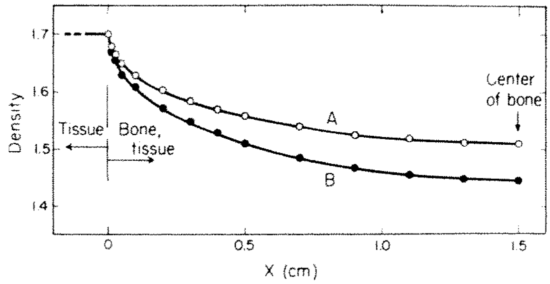

FIG. 3. Photographic density variation in the image of a bone embedded in tissue.
A—Blue Brand Film (direct x-rays). B—No-Screen Film (direct x-rays).

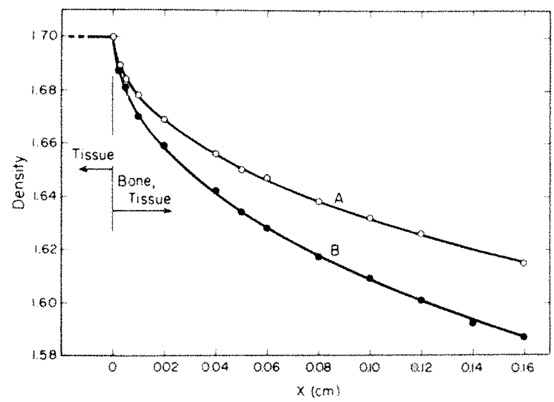

FIG. 4. Photographic density variation in the image of a bone embedded in tissue close to the boundary between bone and tissue. Scale expanded as compared with that in Figure 3.
A—Blue Brand Film (direct x-rays). B—No-Screen Film (direct x-rays).

center. The density gradient is obviously less than if the bone were square in section; further, the over-all contrast is decreased by the presence of tissue. These effects are of different magnitude on the two types of film. It will be shown in a later paper that, in the more practical case of diverging radiation, similar effects occur even when the object being radiographed is a plane parallel plate with a rectangular cross section. From these results it can be understood why it is impractical to express radiographic unsharpness in terms of the distance, measured on the image of an edge, over which the density changes continuously, as mentioned previously. Instead, it is reasonable to state that the subjective impression of sharpness is related to the density gradient at the edge of the image, as has indeed been shown for photographic images. Noting this proposed change in the measure of radiographic unsharpness, we may give the qualitative name "absorption unsharpness" to the subjective impression caused by the physical effects shown in Figure 3.

The density distribution close to the edge is shown on an expanded scale in Figure 4. It can be seen qualitatively how the absorption has reduced the density gradient (*i.e.*, the slope of the curve) as compared to the infinite gradient which presumably would give the impression of perfect sharpness. Using equation (5), one can determine how the density gradient at some fixed distance from the edge varies with the radius of curvature of the edge and with the relative magnitude of the absorption coefficients of the two substances.

From Figure 2 it can be seen that, for the small density range considered in this example, we may write for both types of film,

$$D = K \log E + C,$$

where $K = 2.07$ for Blue Brand Film without screens and $K = 2.77$ for No-Screen Film. Then, from equation (5),

$$D = K \log (I_0 t) - 0.434K \cdot [\mu_1 d + 2(\mu_2 - \mu_1)(2rx - x^2)^{1/2}] + C$$

and the density gradient becomes

$$\frac{dD}{dx} = -0.868K(\mu_2 - \mu_1)\frac{r - x}{(2rx - x^2)^{1/2}}. \quad (7)$$

Letting $r = 1.5$ cm. and choosing $x = 0.01$ cm., a distance which can just be resolved by the eye, we obtain the density gradient as a function of $(\mu_2 - \mu_1)$

$$\frac{dD}{dx} = -7.5K(\mu_2 - \mu_1).$$

Figure 5 shows a plot of this equation for both types of film. The points on the straight line correspond to bone immersed in air, fat and tissue. Values of $(\mu_2 - \mu_1)$ were obtained from Table I.

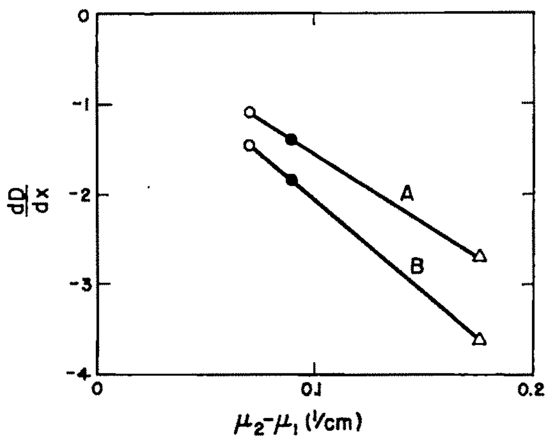

FIG. 5. Photographic density gradient in the image of a bone with 1.5 cm. radius embedded in: △ air; ● fat; ○ tissue. Density gradient measured at a point 0.01 cm. from the edge.
A—Blue Brand Film (direct x-rays). B—No-Screen Film (direct x-rays).

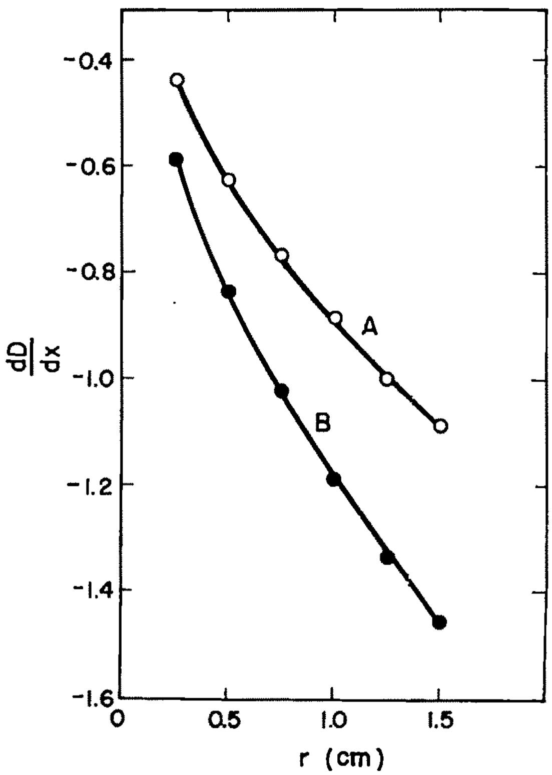

FIG. 6. Photographic density gradient in the image of a bone embedded in tissue as a function of the radius of the bone, measured at a point 0.01 cm. from the edge.
A—Blue Brand Film (direct x-rays). B—No-Screen Film (direct x-rays).

Figure 6 shows a plot of

$$\frac{dD}{dx} = -0.061K\frac{r-0.01}{(0.02r)^{1/2}}$$

obtained from equation (7) for the case of bone in tissue and $x=0.01$ cm.

Accepting the fact that the visual impression of sharpness correlates with the density gradient at the edge of the image, we can conclude from Figures 5 and 6 that sharpness should increase as the difference between linear absorption coefficients of the two bordering substances increases and as the radius of curvature of the object edge becomes larger.

Although the conclusions reached in this study are based on a greatly simplified example, they serve to demonstrate that the concept of absorption unsharpness should be added to the concepts of movement, geometric and screen unsharpness as another physical factor responsible for unsharpness in radiographic images. In fact, absorption unsharpness is peculiar to radiography because it stems from the very basis of radiography, namely, the ability of x-rays to penetrate matter selectively.

SUMMARY

The density distribution across the radiographic image of a cylindrical object has been calculated for an idealized situation, *viz.*, parallel, monochromatic radiation without scatter. The effects of the type of film used, the linear absorption coefficient of the object, and the radius of the cylinder on the density gradient at the edge of the image have been considered. It has been shown mathematically that radiographic "absorption unsharpness" results from absorption of x-rays in the object. An extension of this theory to more practical situations will be presented in the future and will be tested experimentally.

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Eastman Kodak Company
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Forty-third Annual Meeting: Broadmoor Hotel, Colorado Springs, Colo., May 11–14, 1961.

* *Ex officio.*

EDITORIAL

FORD FOUNDATION GRANTS TO THE INTERNATIONAL SOCIETY OF RADIOLOGY FOR THE INTERNATIONAL COMMISSIONS

THE Ford Foundation, on October 10, 1960, announced grants to three important international scientific bodies "to help speed up the task of defining, measuring and limiting hazards resulting from man-made radiation." The International Commission on Radiological Units and Measurements (ICRU) received $185,000. The International Commission on Radiological Protection (ICRP) received $250,000.

The International Bureau of Weights and Measures, established by treaty in 1875, received $32,500; this Bureau is not connected with a Radiological Organization but will assist in the development of world-wide standards of radiation measurement.

The ICRU was established by the First International Congress of Radiology in London in 1925 and the ICRP by the Second International Congress of Radiology in Stockholm in 1928. The members of these Commissions are appointed by the International Congresses, with the advice of Radiation Scientists and Medical Radiologists, on the sole basis of competence and without regard to nationality or political governments. Throughout the past three decades the problems submitted to these Commissions have steadily increased in number and importance. Financial support of their work has not been easy to obtain. Their meetings were usually held every three years in association with the International Congresses.

At the Seventh International Congress in Copenhagen in 1953, the need for additional financial support for these Commissions was obvious, particularly to enable them to meet more frequently than once every three years. Furthermore, at this time there was danger of loss of control of these Commissions by Radiology to another international, pseudogovernmental body. To establish clearly the sponsorship of, and to keep the control of these Commissions under Radiology, direct contributions from an International Radiological Organization were needed, which could not be supplied by the International Congress. For these purposes, the International Society of Radiology was proposed; its organization was worked out by an international committee; it was adopted and put into operation at the Eighth International Congress in Mexico in 1956. A secretariat was established in Copenhagen under the supervision of Professor Flemming Nørgaard, Secretary-Treasurer.

The ICRU and the ICRP then began to operate under the continuing sponsorship of, and to receive financial support from, the International Society of Radiology, in behalf of National Radiological Societies, called "Member-Societies," in thirty-four countries. The importance to the Commissions of this arrangement was reported to the Board of Chancellors of the American College of Radiology in 1958 by Dr. Lauriston Taylor, Chairman of the ICRU; this new sponsorship made Foundations and other sources of funds more receptive to requests for aid. The American College of Radiology became the "Member-Society" representing the United States in the ISR.

The above-mentioned grants will be

issued in annual installments of $37,000 for the ICRU and of $50,000 for the ICRP over a period of five years. The announcement of the Ford Foundation, on October 10, 1960, further stated: "The Foundation's new grants will enable three experienced international agencies to broaden their consideration of radiation problems independent of the policies of governments.

"The International Commission on Radiological Units and Measurements and the International Commission on Radiological Protection have been dealing with radiation hazards since the early uses of x-rays and radium in the 1920's. The Commissions are completely independent, and are neither financed nor sponsored by any government or organization of governments. Their members are selected on the basis of scientific ability without reference to the national interests of their home countries.

"The work of each Commission is carried out largely by committees of scientists and is coordinated through periodic conferences and an international secretariat. The Foundation's grants will help the Commissions meet the increasing demands for their work and will be used for administrative and publication costs, travel funds, and other expenses.

"During the next few years, the International Commission on Radiological Units and Measurements plans to devote major efforts to developing improved units and methods of measuring radiation received by living matter. The methods now widely used are based on the roentgen, a unit that expresses the quantity of energy emitted from a source as x-rays or gamma rays but is of limited value in measuring total doses of radiation absorbed by living organisms.

"The International Commission on Radiological Protection, through its recommendations of safe levels of radiation exposure, has established the basis for the official standards of radiation protection adopted by many countries. In the light of recent scientific developments, it plans to re-evaluate these recommendations and to publish revisions of them."

Dr. Taylor stated, "An essential ingredient in the build-up of our funds has been, and will continue to be, the small but regular support of the International Society of Radiology."

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BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Radiological Examination of the Small Intestine. Second edition. By Ross Golden, M.D., D.Sc., Visiting Professor of Radiology, University of California at Los Angeles; Professor Emeritus of Radiology, Columbia University; Formerly, Director of Radiology, The Columbia-Presbyterian Medical Center, New York City. Cloth. Price, $28.50. Pp. 560, with 176 illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Ave., Springfield, Ill., 1959.

In the review of the first edition of Ross Golden's epoch-making book, "Radiologic Examination of the Small Intestine," the reviewer stated that "this publication marks a milestone in the advance of roentgenology, and should become the constant companion of every roentgenologist who hopes to qualify as such. It is no exaggeration to say that no more important or thought-provoking book has been issued in the field of gastrointestinal roentgenology and such a book would not have been possible without the writer having a thorough knowledge of the recent advances in physiology, neurology and chemical changes during the digestive processes."

The second edition of Doctor Golden's book has just been issued from the press of Charles C Thomas, Publisher. During the intervening years between the first and second editions, Doctor Golden has continued the assemblage of information which he thought to be most helpful in understanding the significance of the examination of the small intestine. In the pages of his book he applies the lessons of anatomy and physiology to clinical problems as they are disclosed by the roentgenologic method of examination.

There has been marked increase in our knowledge of the anatomic structures and the physiology of the small intestine since the first edition. The second edition is greatly augmented in size to incorporate this newly acquired knowledge and it describes how the roentgen-ray studies may contribute to a thorough understanding of the pathologic as well as the normal physiologic processes. Many new chapters have been added which greatly enhance the completeness of the study of the small intestine.

Doctor Golden's intensive studies in internal medicine before he began his career in roentgenology enable him to interpret various phases of the physiologic aspects of the gastrointestinal tract, particularly the small intestine; and he has brought to bear in the current issue of his "Radiologic Examination of the Small Intestine" certain areas of knowledge dealing with the chemical changes in the intestinal tract which add immeasurably to the value of this book.

In the introductory chapter of the second edition, Doctor Golden discusses the potential hazards to health by exposure to roentgen rays during diagnostic procedures, and he points out that any roentgen examination of the human should be carried out by those who are best qualified to protect the patient from excessive radiation. He also points out that, with all due regard for potential dangers from radiation, care must be taken to avoid depriving a patient of the benefit of a roentgen examination which may disclose an immediate hazard to his health or even to his life.

Every roentgenologist and those dealing with the radiologic studies of the gastrointestinal tract can ill afford not to have Doctor Golden's book as a constant companion, as in this book is disclosed all of our present knowledge in its application to a thorough study of the gastrointestinal tract, particularly of the small intestine.

The book has an adequate index which gives ready reference to any given item of interest. It is not only beautifully printed, but the reproductions throughout are of the finest quality. It is with pleasure that one is permitted to review a book of such fascinating interest and importance as this one. To Doctor Golden himself, nothing but thanks and praise should be offered by all physicians who are interested in the gastrointestinal tract for the consummation of such a superb book as the second edition of "Radiologic Examination of the Small Intestine."

Lawrence Reynolds, M.D.

THE YEAR BOOK OF RADIOLOGY (1959–1960 YEAR BOOK SERIES). Edited by John Floyd Holt, M.D., Professor, Department of Radiology, University of Michigan; Walter M. Whitehouse, M.D., Associate Professor, Department of Radiology, University of Michigan; Harold W. Jacox, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Morton M. Kligerman, M.D., Professor of Radiology and Chairman of the Department of Radiology, Yale University School of Medicine; Radiologist-in-Chief, Grace-New Haven Community Hospital. Cloth. Price, $10.50. Pp. 446, with 328 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, Ill., 1960.

This current publication in the series of yearbooks of Radiology upholds the fine traditions and sterling reputation established in past editions. Undoubtedly a majority of radiologists rely on this source for the latest pertinent information and technical developments in their field. The gleaning of the "wheat from the chaff" of radiologic literature has been painstakingly accomplished, and the condensed articles do not lack in readability. A good balance between diagnostic and therapeutic subjects has been obtained.

The editors state that the most popular subject material recently has dealt with biologic hazards of radiation. Angiographic evaluation of carotid and intracerebral atherosclerosis ranks a close second. A number of articles on rare, or foreign, pulmonary diseases are included because of their pertinence at this time of increasing world travel. Among others are those dealing with pulmonary paragonimiasis, bronchiectatic toruloma, and schistosomiasis.

Therapy articles bring recent and encouraging information on marrow transplants in leukemic children, supervoltage treatment of inoperable and recurrent lesions of the rectum and pancreas, melanomas, and soft tissue and osseous sarcomas. Extremely well-selected articles appear in the section on gynecology.

In both the diagnostic and therapeutic sections the editors refer to a number of outstanding articles, monographs, and books which cannot be adequately abstracted and should be read in the original. This of course holds true for any article of particular interest to the individual reader.

An uninterrupted series of these yearbooks of Radiology would seem to be one of the most valuable assets of the radiologist's library.

ARCH H. HALL, M.D.

DIAGNOSTICA RADIOLOGICA DELLE VIE BILIARI. By T. Braibanti, L. Rossi, and A. Maestri; all of the Istituto di radiologia dell'Università di Parma. Pp. 494, with 183 illustrations. Minerva Medica, Turin, Italy, 1958.

This volume is an extended description of the roentgen diagnosis of disease of the gallbladder and bile ducts. In Part I, the authors discuss the preparation of the patient, the examination with and without a contrast medium, the use of extrabiliary contrast, special examinations following transparietal and transhepatic injections of contrast medium, postoperative cholangiography, the study of function, the effects of various drugs on the gallbladder and bile ducts, and the use of roentgen cinematography.

The second part of the book includes discussions of congenital anomalies, calculosis, hydrops, cholecystitis, calcification of the walls of the gallbladder, milk of calcium bile, pericholecystic adhesions, and tumors of the gallbladder and of the bile ducts. A chapter is devoted to functional disturbances of the biliary tract. Obstruction by extrinsic causes is thoroughly discussed and beautifully illustrated, as are internal and external biliary fistulas. An especially interesting chapter concerns so-called regeneration of the gallbladder following cholecystectomy. This is recognized as actually representing incomplete surgical excision. Ninety pages of bibliography close the book.

This volume is noteworthy because of the great detail with which each subject is treated. The authors have had extensive experience in the diagnosis of biliary tract disease, and the correlation of their findings with the observations at surgery is excellent. Some readers may find the length of the book to be excessive.

CESARE GIANTURCO, M.D.

FRACTURES, DISLOCATIONS AND SPRAINS. By Philip Wiles, M.S. (Lond.), F.R.C.S. (Eng.), F.A.C.S., Honorary Consultant Orthopaedic Surgeon, The Middlesex Hospital; Past President of The British Orthopaedic Association, The Orthopaedic Section of The Royal So-

ciety of Medicine, and The Orthopaedic Section of The British Medical Association; Corresponding Member of The American Orthopaedic Association; Formerly, Hunterian Professor of The Royal College of Surgeons of England, Lecturer in Orthopaedic Surgery, at The University of London, and Brigadier, Consultant Surgeon in the Army; British Treasurer of *The Journal of Bone and Joint Surgery*. Cloth. Pp. 67, with 519 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, Mass., 1960.

This is a "jewel" of a book, especially for those studying or teaching roentgenology or orthopedic surgery. An amazing amount of material is presented in only sixty-seven pages, made possible partly by the use of a wide column format with grouping and cropping of the many excellent roentgenograms and the use of outlining in the text whenever possible. The facts are presented in a straightforward manner and in a crisp, brief, typically English style. The sketches which are used have been miniatured but are very clear and explicit. The outlines are used to good advantage to summarize material in certain areas. This book has little resemblance to the author's text book on orthopedic surgery and is much less wordy.

L. Carl Sultzman, M.D.

Low-Level Irradiation. Edited by Austin M. Brues. Cloth. Price, $3.75. Pp. 148. American Association for the Advancement of Science, 1515 Massachusetts Ave., N. W., Washington 5, D. C., 1959.

This volume consists of a collection of eight papers and attendant introductory and conclusive remarks presented at Indianapolis, December 30, 1957, at a symposium of the Section on Zoological Sciences of the American Association for the Advancement of Science under the sponsorship of the United States Atomic Energy Commission and the Division of Biological and Medical Research of the Argonne National Laboratory.

The presentations concerning scientific background deal with: (a) Natural and Artificial Radiation Background of Man (R. A. Dudley), (b) Meteorological Factors and Fallout Distribution (L. Machta), (c) Genetic Effects (E. L. Green), and (d) Somatic Effects (A. M. Brues); those covering implications of low-level irradiation are entitled: (e) Radiation As a Public Health Problem (D. E. Price), (f) Responsibilities of the Press (A. J. Snider), (g) Legal and Political Implications (C. Holifield), and (h) Science and Morality (C. W. Churchman).

The first two papers can be said to cover their subjects adequately and may be considered as true summaries of scientific information. The remaining two in the first section, though necessarily concise because of the broad scope of their contents, reveal the authors' skill in summarizing for the informed layman the status of extemely complex and only partially understood information.

The equally concise section on the implications of low-level irradiation illuminates sharply the impact which they have had upon our authorities and institutions. Readers only partially aware of these problems will find these articles to be worthwhile reading for they discuss the crux of the problem in a matter of fifty pages.

After a brief and useful summary of the conference, the editor brings the volume up to date by commenting on the relevant documentation which appeared in 1958.

L. D. Marinelli

BOOKS RECEIVED

Il Trattamento delle Lesioni Cutanee da Radiazioni. By Prof. Armando Isola, Libero Docente in Radiologia Medica, Istituto di Radiologia della Università di Genova, Genoa, Italy; and Dr. Leopoldo Bosio, Aiuto e Specialista in Chirurgia Plastica, Padiglione Mutilati del Viso, Istituti Clinici di Perfezionamento, Milan, Italy. Cloth. Pp. 218, with 81 illustrations. Minerva Medica, Turin, Italy, 1960.

Atlas of Tumor Pathology; Section IV-Fascicle 10a. Tumors of the Odontogenic Apparatus and Jaws. By Joseph L. Bernier, D.D.S., M.S., F.D.S., R.C.S., (England), Major General, Dental Corps, U. S. Army; Assistant Surgeon General; Chief of Dental Corps, U. S. Army; Former Chief, Oral Pathology Division, Armed Forces Institute of Pathology; Professor and Chairman of the Department of Oral Pathology, Georgetown University School of Dentistry, Washington, D. C. Paper. Price, $1.00. Pp. 107, with 120 illustrations. Armed Forces Institute of Pathology, under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council, Washington, D. C.,

1960. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C.

DIAGNOSTICA RADIOLOGICA DEL CANCRO DELLA MAMMELLA. By G. Pisani, A. Malaspina, and G. Savino. Cloth. Pp. 162, with 140 illustrations. Minerva Medica, Turin, Italy, 1960.

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LARGE RADIATION SOURCES IN INDUSTRY. Volume I. Proceedings of a Conference on the Application of Large Radiation Sources in Industry and Especially to Chemical Processes; Organized by the International Atomic Energy Agency; Warsaw, 8–12 September 1959. Paper. Price, $4.50. Pp. 478, with 300 illustrations. International Atomic Energy Agency, Kärntner Ring, Vienna 1, Austria, 1960. For sale by International Publications, Inc., 801 3rd Ave., New York 22, N. Y.

STRAHLENGEFÄHRDUNG UND STRAHLENSCHUTZ IN DER ZAHNÄRZTLICHEN RÖNTGENDIAGNOSTIK. By Professor Dr. med. Dr. med. dent. Theodor Kirsch, Oberarzt an der Universitätsklinik und Poliklinik für Mund-, Zahn- und Kieferkranke in Heidelberg. Paper. Price, DM 6,80. Pp. 59, with 47 illustrations. Dr. Alfred Hüthig Verlag, Wilckensstrasse 3, Heidelberg, Germany, 1960.

LES RAYONNEMENTS IONISANTS; CALCULS TECHNIQUES; TABLES DE VALEURS NUMÉRIQUES À L'USAGE DES INGÉNIEURS, RADIOLOGUES, OFFICIERS. By Lucien Brunelet, Ingénieur de recherche industrielle. Paper. Price, $2.14. Pp. 74. Gauthier-Villars, Editeur—Imprimeur—Libraire, 55, Quai des Grands-Augustins, Paris (6^{e}), France, 1960.

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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NECK AND CHEST

SUTTON, MAURICE. The functional effect of pulmonary irradiation. *Brit. M. J.*, Sept., 1960, *2*, 838–841. (From: Medical Research Council, Radiotherapeutic Research Unit, Hammersmith Hospital, London, England.)

While a number of workers have studied the effect of postradiation fibrosis on lung function, little is known about pulmonary function during the actual irradiation and in the period prior to the development of pulmonary fibrosis.

A number of patients undergoing irradiation of the lungs either directly, because of carcinoma of the bronchus, or indirectly, in cases of carcinoma of the breast, was subjected to lung function studies before, during and after treatment. The patients received roentgen irradiation from conventional 240 kv. deep roentgen-ray machines or from an 8 mev. linear accelerator. An attempt was made to show the difference in functional effect between the two forms of irradiation.

The author concludes that lung function tends to be depressed toward the end of the course of roentgen therapy at 240 kv. but that such depression was not seen with supervoltage roentgen therapy. This is attributed to the difference in radiation reaction. Moderate functional disability resulting from direct pulmonary irradiation by supervoltage roentgen rays was measured at the end of one year. No real functional disability resulted from roentgen therapy for carcinoma of the breast when modern therapeutic techniques were employed.—*Ralph M. Scott, M.D.*

DOUBLEDAY, LEONARD C. Radiologic aspects of stab wounds of the chest. *Radiology*, Jan., 1960, *74*, 26–33. (Address: 1917 Ashland, Houston 8, Texas.)

In stab wounds of the supraclavicular region a chest roentgenogram, usually taken to determine the presence of pneumothorax, may demonstrate a widened mediastinal shadow resulting from hemorrhage into the mediastinum. Usually, as the pressure in the mediastinum mounts, the mediastinal pleura ruptures and an associated hemothorax develops. Prompt surgical intervention is indicated.

Initial anteroposterior supine roentgenograms of the chest in cases of suspected hemopericardium are difficult to interpret accurately, since it is estimated that 200 cc. of fluid may be present in the pericardial sac without altering the contour of the cardiac silhouette appreciably; however, many cases of proved hemopericardium show a straightened left border of the heart. The rapid accumulation of a relatively small amount of blood in the pericardial sac is sufficient to cause severe symptoms of acute cardiac tamponade which can be diagnosed accurately on clinical grounds when the roentgenologic findings are equivocal. Much larger amounts of fluid may accumulate slowly without causing death and serial roentgenograms may be necessary to detect the accumulation or the recurrence of bleeding or delayed exudative pericardial effusion. Angiocardiography may be necessary to exclude the possibility of persistent pericardial fluid when the cardiac silhouette appears to be within normal limits even in the presence of appreciable amounts of fluid. Although the present consensus of opinion is that hemopericardium is best managed by pericardial aspiration initially rather than by open operation, it would seem rational to believe that an opening in the parietal pericardium should be made as a secondary procedure if there is established evidence of persistent fluid, to permit drainage into the pleural space and to avoid delayed exudative pericarditis and adhesive pericarditis as possible late complications.

In penetrating wounds of the lower thorax, initial roentgenograms of the chest show little of note apart from pneumothorax. An abdominal roentgenogram should be taken initially, and serial roentgenograms of the abdomen and chest often reveal valuable information regarding occult intra-abdominal injury.

Several cases are briefly summarized to illustrate salient features.—*Walter H. Jarvis, Jr., M.D.*

BATESON, ERIC M., and ABBOTT, E. KATHLEEN. Mixed tumors of the lung, or hamartochondromas. *Clinical Radiology*, Oct., 1960, *11*, 232–247. (From: Department of Diagnostic Radiology of the United Sheffield Hospitals and the City General Hospital, Sheffield, England.)

The authors review over 200 previously reported cases of hamartochondroma and report 15 tumors of this type from their personal experience.

The incidence of intrapulmonary hamartochondromas is estimated at 0.04 to 0.33 per cent of autopsies. Sixty-nine per cent occurred in males. Sixty-four per cent were found in the right lung.

Roentgenologically, the tumor is of two types, endobronchial and intrapulmonary. The former is rare, presents with signs of peripheral collapse, and cannot be differentiated from other endobronchial tumors. The intrapulmonary type is described as a well-defined round or oval tumor, most often lobulated and occurring peripherally. Eighty-two per cent are under 5 cm. in size. Irregular calcification was found in one-third of the cases, more often in the larger tumors.

An excellent differential diagnosis is given. It was found that a large mass (over 5 cm. in size) which has a lobulated outline and which contains irregular calcification is most likely a hamartochondroma. This is also a strong possibility in cases of small tumors with well-defined outlines, no calcifications, and no satellite nodularity. The use of laminagraphy

is urged to better outline the tumor and to detect the presence of calcium.—*Barry Gerald, M.D.*

CORNELIUS, EUGENE A., and BETLACH, EUGENE H. Silo-filler's disease. *Radiology*, Feb., 1960, *74*, 232–238. (Address: E. A. Cornelius, Hermann Hospital, 1203 Ross Sterling Ave., Houston 25, Texas.)

Since 1954, sporadic cases of pulmonary disease of unusual etiology have been encountered. The patients have a history of being exposed to nitrogen dioxide, a gas which forms in newly filled silos. Analyses of experimental lots of silage show that nitric oxide is the chief gas produced, which forms nitrogen dioxide upon contact with air. Nitrogen dioxide production reaches a peak within twenty-four hours of the time a silo is filled, and subsides in two or three days. It is a reddish brown gas, heavier than air, and quite irritating.

The illness following exposure is due primarily to the intensity and duration of exposure and secondarily to individual sensitivity. Mild exposure produces a catarrhal inflammation, while more serious exposure results in loss of bronchiolar epithelium, with fibrinous bronchiolar and peribronchiolar inflammation. Acute death from pulmonary edema is due to severe injury of the bronchiolar, alveolar, and capillary walls. Many changes have been observed in less acute cases, including bronchiolitis fibrosa obliterans, alveolar atelectasis, emphysema, bronchopneumonia, and focal interstitial fibrosis. Clinically, the typical illness may occur either as an immediate or a delayed reaction. Of 4 patients who had an immediate reaction, 2 died due to acute pulmonary edema. In the delayed group the illness is triphasic, with the acute phase coming on a few hours after exposure, then variable remission followed by relapse in two to five weeks.

Roentgenographic features have been nonspecific and variable and tend to lag behind the clinical course. Pulmonary edema with bilateral infiltration was observed in 1 case. Two cases of acute bronchopneumonia showed patchy confluent areas of infiltration, chiefly in the midlung fields, with later rapid and complete resolution. Six cases with bronchiolitis obliterans exhibited miliary nodulation at the height of the relapse, with roentgenographic resolution beginning about the fortieth day. One case two and one-half years after exposure exhibited no significant roentgenographic signs, although severe obstructive emphysema was present.

Final diagnosis is dependent on correlation of the history with the clinical and roentgenographic changes. The acute cases may resemble farmer's lung, and the differential diagnosis must be made on the basis of the date of silo filling and the presence or absence of an unusual gas. The delayed cases may be confused with pneumonia or tuberculosis, while bronchiolitis fibrosa obliterans may be differentiated from acute disseminated histoplasmosis by the history, greater clinical severity, smaller nodules, and absence of hilar lymphadenopathy. Metastasis and pneumoconiosis are excluded by nonroentgenographic means.

Treatment consists of the administration of oxygen and prophylactic antibiotics along with bed rest during the acute phase. Adrenal cortical hormone has been of value in treating the delayed cases during the relapse phase.

The authors review the literature of 13 reported cases and add 2 new case reports.—*James C. Moore, M.D.*

PETERSEN, JAMES A. Recognition of infrapulmonary pleural effusion. *Radiology*, Jan., 1960, *74*, 24–41. (Address: Massachusetts General Hospital, Boston, Mass.)

The present study consists of an analysis of 25 selected cases of infrapulmonary pleural effusion. Ten cases were associated with heart disease, 7 with malignant neoplasm, 4 with hypoproteinemia (nephrosis, cirrhosis), and 4 with inflammatory pulmonary or pleural disease. In 5 patients the process was bilateral; in the 20 with unilateral involvement, the effusion was on the right side in 14 and on the left in 6.

Typically, an infrapulmonary effusion presents itself on the posteroanterior upright projection as an apparently elevated leaf of the diaphragm, with a contour similar to a diaphragmatic shadow and just as dense. A characteristic form of this pseudodiaphragmatic shadow has previously been described as showing a gradual inclination upward and laterally from the cardiac shadow, with a rather abrupt drop near the costal margin to form a sharp gutter similar to a normal costophrenic angle; however, this occurred in less than 50 per cent of the cases studied. Recognition of the effusion on the left side is usually not difficult because of the unusual separation of the lung and the gas bubble in the stomach. In the lateral upright projection the pseudodiaphragmatic shadow is again seen, but more often only the midportion of the upper margin of the fluid is rounded and the posterior gutter is filled. An infrapulmonary effusion appears to reduce the volume of the lower lobe of the normal lung, while the remaining lobe or lobes seem to be unchanged in size and position. This produces a rather characteristic configuration on the upright lateral roentgenogram where the convex upper margin of the fluid meets the major fissure, forming a straight component of the pseudodiaphragmatic shadow anteriorly. In many cases the linear shadow of the major fissure above the effusion appears widened by the fluid entering the fissure. Lateral decubitus and supine roentgen studies may also be used to demonstrate the amount of hidden effusion, its mobility, and the true position of the diaphragm. Pneumoperitoneum

with upright roentgenograms may also be used to delineate the true level of the diaphragm and the exact level of the fluid. Fluoroscopy in the upright position ordinarily shows that diaphragmatic mobility is not impaired and that the upper border of the fluid maintains its contour and transmitted mobility; however, with suspended respiration, the upper shadow of the fluid may be seen to "shimmer" or undulate due to agitation by normal cardiac motion and, with deep expiration and lateral tilting, the fluid may be observed to spill out into the gutters and to assume the more usual appearance of pleural effusion.

The exact nature of the forces responsible for localizing fluid in this peculiar position is not known. In general, it is agreed that gravity is proabably the main factor when there is a pleural space that is free of adhesions and a healthy lung above.—*W. H. Jarvis, Jr., M.D.*

Bulgrin, James G., Dubois, Edmund L., and Jacobson, George. Chest roentgenographic changes in systemic lupus erythematosus. *Radiology*, Jan., 1960, *74*, 42–49. (Address: G. Jacobson, 1200 N. State St., Los Angeles 33, Calif.)

Systemic lupus erythematosus is a chronic disease subject to spontaneous remissions and exacerbations. A single organ system may be affected but the disease characteristically involves many organ systems resulting in extremely varied clinical manifestations. In recent years attention has been focused on the chest roentgenographic findings in this disease primarily because of conflicting opinions regarding the specificity of observed roentgen changes. The published reports, including single cases and large series, show disagreement both as to the frequency and type of roentgen findings. In general, the larger series of cases indicates that the roentgen changes are not specific.

Because of the conflicting reports, the authors conducted a study of the chest roentgen findings in 207 cases of lupus erythematosus. This study constitutes the largest reported series to date. The cases were classified as to the single and combined pleural, cardiac and pulmonary changes and the findings were further correlated with the duration of the disease.

The observed pleural changes consisted of effusion or pleural thickening and were present as an isolated abnormality as well as in combination with cardiac or pulmonary involvement. The abnormal cardiac changes consisted of nondistinctive enlargement, either isolated or combined with pleural and/or pulmonary involvement. The pulmonary changes were variable and nonspecific. Three cases exhibiting the variability of the pulmonary lesions are reported: one with infiltrative changes; one with manifestations of pulmonary edema; and one with extremely varied serial changes including the transient appearance of spherical lesions, one of which showed cavitation. It is interesting to note that no abnormality was present in 96 cases (46.6 per cent) which were not limited to the earlier stages of the disease.

The authors conclude that, due to the great variability in the reported series, one must be cautious in drawing conclusions on the basis of a single roentgenographic study. Although it is unusual, systemic lupus erythematosus may be present for many years and may even terminate fatally without a roentgenographically demonstrable thoracic abnormality. Combined involvement of the heart, pleura and lung is much more common than a single system involvement. Also, there seems to be a greater tendency for rapid change in pleural effusion and heart size in multisystem involvement than when the heart, pleura or lung is affected singly. Involvement of the lungs is less frequent than that of the heart or pleura and is not specific for the disease.—*Edward B. Best, M.D.*

Freimanis, Atis K., and Molnar, William. Chronic bronchitis and emphysema at bronchography; survey of diagnostic features obtained by reviewing 2,000 bronchograms. *Radiology*, Feb., 1960, *74*, 194–205. (Address: W. Molnar, Department of Radiology, Ohio State University Health Center, Columbus 10, Ohio.)

The purpose of this paper is to draw attention to the manifold bronchographic features of chronic bronchitis found in a study of 2,000 bronchographic examinations performed in a five year period at the Ohio State University Hospital.

The bronchographic criteria of chronic bronchitis vary greatly in range and quite frequently a variety of changes will be found simultaneously in one patient. The following changes have been observed in patients with chronic bronchitis and emphysema: (1) *Spasm.* On the bronchogram it is seen as a narrowing of the lumen with a gradual transition to normal caliber, and the extent of involvement varies greatly. The differentiation of spasm from organic obstruction may be made by close observation or repeated examination. (2) *Emphysema.* Bronchographic features include the "leafless tree" appearance, separation of the bronchial branches from each other, widening of the peripheral zones into which filled bronchial branches do not extend, bending and displacement of bronchi around emphysematous blebs, and thinnning of the peripheral bronchial branches. (3) *Increased and abnormal secretion.* This is indicated by defects along the bronchial wall or nonfilling of part of the bronchial tree. (4) *Obstruction.* This may be due to spasm, secretion, or disease causing destruction of the bronchial wall with subsequent scarring and obliteration of the lumen, in which case the differentiation between nonspecific inflammatory obstruction and neoplastic or specific inflammatory

obstruction (*e.g.*, tuberculosis) is difficult and usually has to be made on the basis of secondary evidence. (5) *Patchy alveolization.* This is due chiefly to obstruction or different rates of air flow in the smaller branches of the bronchial tree. The regular peripheral filling can range from relatively mild uneveness to a striking major "patchiness" of filled peripheral bronchioles and confluent alveolar filling with large surrounding areas devoid of any contrast material. (6) *Bronchiectasis.* This is the result of localized destruction of bronchioles with "pools" or "bronchiolectases" appearing as small round collections of contrast material. Occasionally there is cylindrical dilatation. "Spiders," possibly better called "peripheral shadows with spiked outline," are similar in origin and represent filled dilated bronchioles with several distended side branches and without further peripheral filling. (7) *Irregularity and deformity of the bronchial wall.* This is due to localized mucosal destruction, localized dilatation of the bronchial lumen, and fibrotic contractions in the more severe cases of chronic bronchitis. Initially the process may cause only irregularity of the bronchial outline. (8) *Dilatation of the larger bronchi.* Remarkable localized dilatations of some of the terminal branches may be found in association with chronic bronchitis, and represent an unusual type of bronchiectasis. (9) *Atrophy of the bronchial mucosa.* This is manifested by the appearance of annular areas of slight widening and narrowing of the lumen, thought to be the result of atrophic thinning of the mucosa. (10) *Mucous gland dilatation.* The distended mucous glands are usually seen as small extensions of contrast medium beyond the lumen of the bronchus, most often in the walls of the major bronchi. Their presence on bronchograms is characteristic of chronic bronchitis. (11) *Bronchial and tracheal inflammatory diverticula.* Rarely, multiple diverticula of the trachea are found. Single diverticula of the trachea or major bronchi are found more commonly, and are usually the result of a developmental error in the branching of the bronchial tree.

The pathologic findings obtained during bronchography are evidence of functional as well as morphologic changes and may provide detailed information necessary for accurate diagnosis and better understanding of the process. Through the use of bronchography valuable information may be obtained about an extensive part of the bronchial tree not accessible to other examinations.—*Walter H. Jarvis, Jr., M.D.*

Janin, P. (Grenoble, France.) Intérêt de l'angiocardiographie dans l'étude des malformations pulmonaires. (The value of angiocardiography in the study of pulmonary malformations.) *J. de radiol., d'électrol. et de méd. nucléaire*, Sept., 1960, *41*, 432–439.

Cases are cited and roentgenograms are reproduced to show how angiocardiography may be of help in the diagnosis and demonstration of pulmonary malformations. Agenesis and hypoplasia of the lung, sequestration, abnormal venous returns, and some abnormalities involving emphysema or other forms of abnormal air retention are demonstrated. The angiocardiographic findings are not only of value in helping to make the diagnosis but are of great aid to the surgeon in helping predict the anatomic findings before surgery is contemplated.—*Charles M. Nice, Jr., M.D.*

Dalith, F., and Neufeld, H. Radiological diagnosis of anomalous pulmonary venous connection: a tomographic study. *Radiology*, Jan., 1960, *74*, 1–18. (Address: F. Dalith, Government Hospital, Tel-Hashomer, Israel.)

An anomalous pulmonary venous connection is a congenital malformation in which one, several, or all of the pulmonary veins empty into the right atrium or one of its tributaries. This anomalous connection may be partial, in which case one or several, but not all, of the pulmonary veins empty into the right atrium or a systemic vein. Or the anomaly may be total, in which case all the pulmonary veins empty into the right atrium. The diagnosis of this anomalous connection is important as it is one of the anomalies responsible for a left to right shunt that is amenable to surgical treatment. Knowledge of the presence of this anomaly will also be of value to the surgeon doing cardiac or lung surgery.

The authors present a comprehensive review of the literature concerning this anomaly. In addition, a study is presented based on 9 patients in whom different types of the partial form and one of the total form of the anomaly were found. In this study the use of laminagrams was relied upon extensively to show the abnormal vascular morphologic details and to demonstrate the associated bronchopulmovascular malformations. This procedure may delineate clearly a disordered vascular pattern, the regions drained by the anomalous veins, the areas of lung traversed by them, the site of connections, and the width and shape of the vessels.

The authors stress, however, that although a surprisingly detailed anatomic diagnosis can be achieved by laminagraphy it cannot be relied upon alone if surgical treatment of this anomaly is planned. This is because not all forms of anomalous pulmonary venous connections can be demonstrated by this technique. Also, the presence of any associated malformation, the most common of which is an atrial septal defect, can only be demonstrated by other means such as cardiac catheterization and angiocardiography.—*Donald N. Dysart, M.D.*

Broustet, P., Wangermez, Ch., Duhamel, J., Martin, P. L., Bricaud, H., and Fontanille, P. (Bordeaux, France.) Étude com-

paratiwe des résultats des mesures du volume cardiaque par la méthode de stratigraphie axiale transverse et les méthodes géométriques téléradiographiques. (Comparative study of the results of measurements of cardiac volume by the method of transverse axial stratigraphy and teleradiographic geometric methods.) *J. de radiol., d'électrol. et de méd. nucléaire*, Sept., 1960, *41*, 417–431.

Several teleroentgenographic geometric methods for determining cardiac volume are cited, giving errors of about 6–16 per cent. These methods were compared with one using axial laminagraphy. Although the error is less than 10 per cent with the laminagraphic method, the other procedures are probably easier to carry out and have about the same degree of reliability.

It is concluded that cardiac volume is of more value in studying the evolution and prognosis of disease than in the original diagnosis.—*Charles M. Nice, Jr., M.D.*

Wolf, Bernard S. Roentgen features of the normal and herniated esophagogastric region. *Am. J. Digest. Dis.*, Sept., 1960, *5*, 751–769. (From: Department of Radiology, The Mount Sinai Hospital, New York, New York.)

Recognition of a sliding hiatus hernia more than 3 cm. in size presents little difficulty to the examiner. Below this size it is much harder to demonstrate, especially if the functional and anatomic regions of the distal end of the esophagus are not well known. In this article a detailed description of this area is presented. The author also emphasizes use of the epithelial ring to demonstrate small hiatus hernias.

Templeton's phrenic ampulla is discussed and it is pointed out that, of all the various sized sacs occurring during this phenomenon, the smallest sac that may persist and retain barium is *the* phrenic ampulla. This phrenic ampulla is enclosed above by the inferior esophageal sphincter (which is located approximately 1.5 to 2 cm. above the diaphragm hiatus) and below by the submerged segment. The upper level of the submerged segment is normally found at the diaphragm hiatus. The submerged segment itself is about 2 cm. long. Its distal end, called the cardiac antrum, merges into the stomach. In patients with hernias, the pinchcock action of the diaphragm can be used to indicate the level of the hiatus.

In reviewing Templeton's and Schatzki's rings, the author states that he feels both are anatomic gradations of the same thing, namely, the esophagogastric epithelial junction. He feels that demonstration of this ring above the hiatus is diagnostic of hiatus hernia.

In some patients with hiatus hernia the vestibule, which is composed of the phrenic ampulla and the proximal portion of the submerged segment, can be exactly delineated if both the inferior esophageal sphincter above and the esophagogastric junction below can be demonstrated. If the epithelial ring is not prominent, the vestibule and hernia appear as one sac. Under normal conditions, the vestibule is usually not evident as a single distensible region. However, sometimes it may be seen as a long empty segment between the esophageal segment and the distal portion of the submerged segment. It corresponds roughly to the sphincteric segment in the distal 4 cm. of the esophagus.—*William W. Joule, M.D.*

Abdomen

Leger, Lucien, and Crismer, Roger. Le radiodiagnostic des pancréatites chroniques. (The roentgen diagnosis of chronic pancreatitis.) *Acta gastro-enterol. belg.*, May–June, 1960, *23*, 396–449.

In a rather lengthy but meticulous manner the authors present the various roentgen examinations and findings for chronic pancreatitis.

1. Plain roentgenograms. Two types of calcification are noted: (a) Rather large calcifications about 10 mm. in diameter, with only one or a few located in the ducts; and (b) minute multiple calcareous deposits which may be either intracanalicular or within the parenchyma as part of a degenerative process in pancreatic tissue. These are best seen using both the anteroposterior and lateral projections.

2. Roentgen changes in the stomach and duodenum. When there is enlargement of the pancreas, such changes are distinct, but if the pancreas is atrophic and small there may be no demonstrable changes. The following are among the abnormalities to be looked for: (a) antral bulbar duodenitis, or antritis and duodenitis; (b) widening of the duodenal loop, which may be difficult to differentiate from carcinoma of the head of the pancreas; (c) deformity of the inverted "3" type, caused by pressure of the expanding head. (This also may be difficult to differentiate from carcinoma of the head of the pancreas.); (d) stenosis of the descending duodenum, which may also be seen with carcinoma of the head of the pancreas; and (e) edema and enlargement of the papilla of Vater.

When lesions involve the body and the tail of the pancreas there is enlargement of the retroperitoneal or retrogastric space with compression of the body of the stomach, deformity or displacement. There is disturbed motor function of the duodenum as well as of the antrum with irregular accentuation of the folds.

3. Roentgen signs following oral and intravenous cholangiography. In the absence of cholecystitis, with normal liver function, studies of the ducts present the following: (a) diffuse retraction, which is uni-

form or rectilinear in appearance, of the pancreatic and retropancreatic portion of the common bile duct; and (b) stenosis involving the region of the papilla with proximal dilatation of the common duct. The dilated duct often presents a right sided concavity due to pancreatic hypertrophy between the duodenum and common bile duct. This may not necessarily be diagnostic of pancreatitis as it may occur in carcinoma as well.

When oral or intravenous cholangiography is not feasible, the common duct may be visualized by transhepatic or peritoneoscopic cholangiography.

4. Laminagraphy following gastric and retroperitoneal insufflation. Using air in the stomach anteriorly and nitrous oxide for retroperitoneal insufflation posteriorly, the pancreatic mass is clearly defined anterior to the vertebral bodies.

5. Splenoportography. The value of this study is based on the close relationship of the splenic vein with the tail and body of the pancreas, and of the portal vein with the head of the pancreas. In chronic pancreatitis the splenic or portal venous systems are involved with compression and distortion occurring and with resultant hypertension as determined by manometric studies.

6. Pancreatography. This may be done by transparenchymal puncture into the main duct when it is dilated, by catheterization of the duct during a left hemipancreatectomy, or by transduodenal catheterization of the duct without prior sphincterectomy. The opacified duct will show such pathologic changes as dilatation, irregularity, narrowing, and constriction, as well as stenosis.—*William H. Shehadi, M.D.*

Baker, Hillier L., Jr., and Hodgson, John R. Further studies on the accuracy of oral cholecystography. *Radiology*, Feb., 1960, *74*, 239–245. (Address: H. L. Baker, Jr., Mayo Clinic, Rochester, Minn.)

In order to discover the degree of accuracy of cholecystographic diagnosis in the year 1957, the operative and pathologic findings of all surgically treated patients on whom cholecystograms had been obtained were correlated with the roentgen diagnoses. A total of 1,207 patients were available for this study. All these patients had been examined with the use of iopanoic acid (telepaque). The accuracy of the diagnoses in this series was then compared to that of two previous series in which iodoalphionic acid (priodax) only and iodophenoxic acid (teridax) only were used.

The results of this study showed that only 1.9 per cent of all diagnoses were found to be in error compared to 2.7 and 2.4 per cent error in the two previous series. This reduction in error was felt to be the result of eliminating the "avoidable" errors discovered in the earlier series and thus improving diagnostic accuracy. The use of iopanoic acid increased the number of gallbladders observed with higher concentrations of medium but there was no evidence that this increased opacity obscured tiny calculi or permitted visualization of abnormal gallbladders which did not contain stones.

An improvement in roentgenographic technique and interpretation was thought to account for the correct diagnosis of normally functioning gallbladders in 98.3 per cent of these cases. Fewer gallbladders were called "poorly functioning," apparently due to the use of the newer medium, iopanoic acid, and those that were given that diagnosis (3 cases) were found to be diseased.

Stones were found in 98.0 per cent of the cases diagnosed preoperatively as cholelithiasis. This is a slight decrease in accuracy from the previous series and was thought to be due to the misinterpretation of the findings made available as a result of the increased opacity of the medium. Polyps, papillomas, or adenomas were found in all cases in which they were reported. Among the gallbladders reported as nonfunctioning, 97.8 per cent were found to be diseased. This showed no change in the incidence of normal gallbladders in the nonfunctioning group.

The authors discuss in detail their actual procedure of cholcystography, including the preliminary preparation of the patient, the roentgenographic technique and positioning of the patient. Useful technical adjuncts such as the use of dihydroxyphenylisatin as a purgative, the use of a recently purified form of cholecystokinin to cause gallbladder contraction, and the use of radiolucent plastic foam blocks to afford compression of the gallbladder area are mentioned.—*D. N. Dysart, M.D.*

Genitourinary System

Abeshouse, Benjamin S., and Abeshouse, George A. Sponge kidney: a review of the literature and a report of five cases. *J. Urol.*, Aug., 1960, *84*, 252–267. (Address: B. S. Abeshouse, Urological Department, Sinai Hospital, Baltimore 5, Md.)

The sponge kidney is a term applied to a rare disease of the kidney first described in 1939. The present authors review the literature, from which they have collected 131 cases, and they add 5 personal cases.

The most striking pathologic feature of this disease is the presence of multiple small cystic cavities (1 to 3 mm. in diameter) confined to the pyramidal portion of one or both kidneys. These cysts may be spherical or irregular and are lined with pyramidal, cuboidal, or flat epithelial cells. The contents may be a clear fluid or fluid containing crystalline salts of calcium or varying sized calculi. Since the cysts connect with the pyelocalyceal system, they may be opacified by contrast substances used in pyelography. In the early cases, the kidney may be normal

or slightly larger than normal with no alteration in function. In later cases, deformity caused by calyceal compression from the pyramidal cysts or by infection, stone formation, pyelonephritis, and hydronephrosis may be seen on the pyelogram.

The etiology of this condition is not clearly understood but it is the consensus of opinion that faulty ontogenetic development is involved.

Sponge kidney is more frequent in males than in females and more frequently is bilateral than unilateral. Calculi are present in the majority of cases when first seen, probably because they are the factor which calls the attention of the patient and the physician to an abnormal kidney.

The diagnosis of sponge kidney may be made by intravenous or retrograde pyelography which will reveal the characteristic clusters of dye-filled cysts in the involved renal pyramids or the calculi in this distribution. Differentiation must be made from the microcystic form of polycystic disease, calyceal diverticula, ureteritis cystica, acute and chronic pyelonephritis with cystic changes, pyelogenic cysts, renal tuberculosis with cysts, nephrocalcinosis, and pyelotubular transflow.

No specific treatment is known for uncomplicated cases of sponge kidney. Usually these patients are asymptomatic until the development of some complication of infection, obstruction or stone and these complications are treated by the customary means. It is important, however, that the basic underlying pathology be recognized.—*George W. Chamberlin, M.D.*

Harrow, Benedict R., and Sloane, Jack A. Polycystic renal disease with renal and splenic artery aneurysms. *J. Urol.*, Sept., 1960, *84*, 447–452. (Address, B. R. Harrow, 2621 Biscayne Blvd., Miami, Fla.)

The present evidence indicates that the most likely cause of polycystic renal disease is a developmental defect in the germ plasm leading to numerous cystic formations in nephrons.

Polycystic disease of the kidney is associated with cystic disease of the liver and pancreas and with "berry" aneurysms of the cerebral vessels. Such congenital defects may be transmitted by a dominant autosomal gene.

A case report is included to illustrate the coincidental finding of left renal artery aneurysm, left splenic artery aneurysm, polycystic disease, and hypertension in a thirty-seven year old female. The questions which arose in the clinical evaluation and handling of this patient were: (1) should aortography be used to verify the finding of a ring calcification in the splenic artery region; and (2) should surgical treatment be utilized for a proved aneurysm?

It may be advisable to use aortography in young people with hypertension when there is a reasonable chance of repairing or grafting the renal artery. In these patients who have polycystic renal disease, nephrectomy is contraindicated.

The incidence of aneurysms of the renal and splenic arteries has probably been considered to be lower than recent facts indicate. Careful dissection of these vessels at autopsy and further evidence disclosed by aortography points toward a more accurate identification of these lesions.—*George W. Chamberlin, M.D.*

Hill, J. Edward, and Bunts, R. Carl. Thoracic kidney: case reports. *J. Urol.*, Sept., 1960, *84*, 460–462. (Address: J. E. Hill, Medical Arts Building, Richmond 19, Va.)

The authors present 3 patients in whom the left kidney was in an abnormally high position. This was visualized, on the roentgenogram, as a dome-shaped soft tissue mass in the left posterior thorax which might be mistaken for a hernia, neurofibroma or pleural cyst. The retrograde pyelogram demonstrated an elongated ureter with a high kidney showing a normal calyceal system. In one instance a pneumoperitoneum helped to make the correct diagnosis. This condition represents a congenital anomaly which may be associated with a herniation through the foramen of Bochdalek or a congenital eventration of the posterior leaf of the diaphragm.—*George W. Chamberlin, M.D.*

Fine, Myron G., and Vermooten, Vincent. Spontaneous extravasation associated with excretory urography. *J. Urol.*, Aug., 1960, *84*, 409–413. (Address: M. G. Fine, 616 Medical Arts Building, Dallas, Texas.)

The authors present 3 patients in whom extravasation of contrast medium was noted on intravenous pyelograms. All cases had ureteral colic and, in 2 instances, opaque calculi obstructed the ureteropelvic junction.

In the discussion of this phenomenon, the various studies of Hinman and Narath were noted. The authors believe that the lymphatics of the kidney play an important role in the drainage of the pelvic contents and may, in fact, act as a safety valve. When an excessive burden is placed upon the renal excretory system, a small lymphatic rupture may occur with spread of the contrast medium into the renal sinus, Gerota's capsule, and the peripelvic and periureteric areas.

The literature contains 32 cases of extravasation of intravenously injected opaque medium similar to those described in this article. Conservative management is recommended unless the subsequent physical signs and symptoms warrant further intervention. Three composite illustrations show the intravenous pyelographic extravasation.—*George W. Chamberlin, M.D.*

ROONEY, DONALD R. Post-voiding films as an aid to opacifying the obstructed ureter. *J. Urol.*, Aug., 1960. *84*, 300–306. (Address: Department of Radiology, Kennestone Hospital, Marietta, Ga.)

In this paper the author succinctly points out the value of a post-voiding roentgenogram in those instances of ureteral obstruction in which the site of the obstruction is not identified on the routine supine roentgenograms during intravenous urography. The technique consists of the simple expedient of allowing the patient to walk to the urinal and return to the x-ray room for a post-voiding roentgenogram. This procedure combines the advantages of delay in time, the use of gravity and agitation, and the change in ureterovesical pressures associated with micturition, all of which tend to enhance the value of subsequent roentgen studies. In the event that the patient is not ambulatory, the act of or effort at micturition may give added urologic information on the intravenous study.

Six composite illustrations of intravenous pyelograms are presented to illustrate the value of the method.—*George E. Chamberlin, M.D.*

BANSBACH, WILLIAM A., MAY, ROBERT E., and BOGASH, MORTON. Hypotonic bladder associated with sickle cell trait. *J. Urol.*, Sept., 1960, *84*, 470–471. (From: Surgical Service, Section of Urology, Veterans Administration Hospital, Philadelphia, Pa.)

The authors have found 4 patients with vesical hypotonia among 16 patients with sickle cell anemia. All patients were examined because of hematuria, which is not an uncommon sign in cases of sickle cell anemia. Cystometry revealed a greatly enlarged bladder (capacity, 1,100 ml.) with weak detrusor urinae contraction and reduced proprioception on bladder distention. No vesical neck obstruction was present.

In these patients with diminished sensory perception, the differential diagnosis should also include pernicious anemia, tabes dorsalis, and other spinal cord disease. The authors postulate that ischemic infarcts in the nervous system may cause bladder hypotonia, but the exact mechanism has not been identified.—*George W. Chamberlin, M.D.*

CHEYNET, M. MAURICE. Étude radiologique de la bilharziose urinaire. (Roentgenologic study of urinary bilharziasis.) *J. d'urol., Paris.*, April, 1960, *66*, 237–253.

Infestation with *Schistosoma haematobium* (bilharziasis) is very often associated with urinary involvement. The lesions are usually located in the terminal ureter, with stasis proximal to it. The resulting hydronephrosis leads to interstitial nephritis, frequently with irreversible parenchymatous damage. It is very important to know that these lesions are commonly asymmetric which permits surgery to be considered. However, it is better, if possible, to re-establish ureteral patency at an early stage, and thus to save the kidney.

The roentgen appearance, without a contrast medium, may be typical, inasmuch as the calcified parasitic ova deposited in the wall of the urinary bladder and in the lower ureters present very characteristic irregular ribbon-shaped, interlaced opacities interspersed with nodules of various densities and projected over the entire area of the urinary bladder.

After intravenous opacification of the urinary tract one may study the pelviocalyceal dilatations, although they are not characteristic. As stated above, the ureteral strictures as a rule are located in the distal two to three inches near the cystoureteral junction and in the vicinity of the calcifications which indicate the presence of ova.

There are millions of individuals suffering from urinary bilharziasis. Most of them reside in the tropics but, with modern transportation, one may find such a case in a temperate climate. The author, who lives in Madagascar, studied 43 patients with bilharziasis and in 29 of them he could demonstrate the existence of urinary tract involvement. In 9 patients, severe damage was found. Because symptomatology is very insidious, irreversible anuria may at times be the presenting symptom. Consequently, all patients known to have bilharziasis should have a thorough urinary examination, including intravenous pyelography.—*E. R. N. Grigg, M.D.*

SKELETAL SYSTEM

LEGRÉ, J., and SERRATRICE, G. (Marseille, France.) Aspects radiologiques des tumeurs primitives du rachis et leur traitement; (à propos de quarante observations). (Radiologic aspects of primary tumors of the spine and their treatment; [report of 40 cases].) *J. de radiol., d'électrol. et de méd. nucléaire*, May, 1960, *41*, 217–229.

Primary tumors of the spine are much less frequent than the secondary ones, which explains why they are not as well known. The authors were able to collect 40 cases of their own, all with histologic proof.

They have classified these tumors according to their tissue origin into: (1) tumors from skeletogenetic tissues (osteochondroma, chondroma, and the more exceptional tumors, osteoma, lipoma and periosteal fibroma); (2) tumors from reticulogenetic tissues (reticulosarcoma or Ewing's sarcoma, and plasmocytoma); (3) tumors of vasculo-connective origin (angioma, myeloplax tumor, and aneurysmal bone cyst); and (4) vestigial tumors (vestigium of notochordae).

These tumors were further classified based on the following factors:

Type. (1) In the osteolytic type, especially encountered in malignant tumors, the lysis may be localized or it may produce a partial vertebral collapse or, when more advanced, a complete collapse. Sometimes it may assume a pseudocystic pattern. (2) The proliferative type, observed mostly in benign tumors, may vary in form from a localized condensation to a proliferative neoplasm.

Location in the vertebral structure. (1) In the anterior three-fourths of the vertebra (22.5 per cent of their cases), it may produce a simple local osteolytic notch or, at a later stage, it may lead to a cuneiform vertebra. (2) The intermediate zone (45 per cent of their cases), including the posterior one-fourth of the vertebra and the pedicles, proved to be the most frequent site of the tumors. This area embryologically contains the intermediary ossification centers. The involvement of one or both pedicles will give on the anteroposterior roentgenogram a "one-eyed or blind" vertebra. On the lateral view, a lytic marginal notch may be seen on the posterior aspect of the vertebra. (3) Posterior location (7.5 per cent of their cases) is less frequent and usually the tumors are of the benign proliferative types.

In general, primary malignant tumors rarely give a characteristic picture and are confused with secondary malignant tumors, whereas the findings in many benign tumors are pathognomonic. The axis and curvature of the spine are little affected; there is no great gibbosity with the acute angle such as that produced in Pott's disease and little if any scoliosis or kyphosis is present. Moreover, the intervertebral disk is usually spared.

A detailed roentgenologic study of the various tumors is presented by the authors. They discuss in the malignant group, plasmocytomas, sarcomas and chordomas; and in the benign group, giant cell tumors, aneurysmal bone cysts, angiomas and chondromas.

In the therapeutic considerations, the authors discuss the role of surgery or radiation therapy used separately or combined. The results obtained with each of these techniques are presented.—*H. P. Lévesque, M.D.*

Wholey, Mark H., Pugh, David G., and Bickel, William H. Localized destructive lesions in rheumatoid spondylitis. *Radiology*, Jan., 1960, *74*, 54–56. (Address: M. H. Wholey, Mayo Clinic, Rochester, Minn.)

Certain patients with rheumatoid spondylitis show striking destructive changes involving the intervertebral disks and adjacent vertebral bodies. The changes closely resemble some type of infection such as tuberculosis, brucellosis, or a pyogenic condition. It is believed that the involvement of the intervertebral disk and adjacent bodies represents destruction by a chronic inflammatory process resulting from the spondylitis.

This manifestation of the disease is not widely recognized. Over a period of ten years (1947 to 1956), 10 patients with far advanced rheumatoid spondylitis and roentgenologic evidence of involvement of an intervertebral disk and adjacent vertebral bodies have been seen at the Mayo Clinic. The localized destructive lesions in all 10 cases were similar roentgenologically. Biopsy of the affected area in 2 patients showed chronic inflamatory lesions. In all cases the lesions failed to show the progression that would be expected of other infectious or granulomatous processes. In one patient there was evidence of spontaneous healing without specific treatment. All the patients were men. The average age at onset of symptoms was twenty-four years. In all instances, the disease had been in progress for at least ten years before exaggerated localized pain in the back led to further investigation. Roentgen examination then revealed destruction of the intervertebral disk and the margins of adjacent vertebrae. Destruction of the vertebral bodies was most pronounced anteriorly. Early destruction was soon followed by osteosclerosis of the affected segment.

One patient showed spontaneous resolution and subsequent ankylosis. In another patient, bone graft and fusion produced bony healing and relief of pain. All other patients were treated conservatively with a combination of body casts, antirheumatic drugs, and physical or roentgen therapy.

Three typical cases are reported in detail.—*Arno W. Sommer, M.D.*

Blood and Lymph System

Basu, S. P. Lymphangiography and venography in chronic filarial lymphoedema. *Indian J. Radiol.*, May, 1960, *14*, 89–98. (From: School of Tropical Medicine, Calcutta, India.)

The author studied the veins and lymphatic vessels in chronic filarial lymphedema. Lymphangiography was done in 33 patients with lymphedema and in 4 normal controls. The technique consisted of a preliminary subcutaneous injection of 11 per cent patent blue-V in distilled water given distal to the site of exploration. This stained the lymphatics so that they looked like blue threads when they were exposed by a skin incision. Seventy per cent diodone was rapidly injected into a vessel using a No. 16 or No. 18 needle. Roentgenograms were taken immediately and at two, five and eight minutes after injection.

In lymphedema of the scrotum, an incision was made at the junction of the scrotum and thigh, and 7 cc. of diodone was injected. There was good visualization of the lymphatics in 19 patients. Poor filling occurred in 5 patients with advanced disease. The opacified lymphatics were dilated and tortuous. The changes were most marked in the early stages of the

disease. In more advanced cases saccular dilatations and sudden narrowing were observed, but in general the opacification was poor. In early stages there was filling only on the side of injection and there was partial obstruction at the inguinal lymph nodes. With more advanced disease there was bilateral filling of the scrotal lymphatics due to collaterals and there was complete obstruction in the inguinal region on one or both sides. In later stages of the disease there was no filling or poor filling.

In studies of the lower extremity, 12 cc. of 70 per cent diodone was injected into a lymphatic vessel in front of the medial malleolus. In 6 patients the lymphatics were numerous and were markedly dilated and tortuous. Retrograde filling was observed, whereas this was not present in the 4 normal controls. The site of obstruction was in the mid-thigh and in no case was there opacification of the inguinal lymph nodes. In 2 patients with hard non-pitting edema there was little or no opacification of the lymphatics.

The breasts of 1 patient were studied by injecting 10 cc. of 35 per cent diodone into one of the skin vesicles (dilated lymphatics). In the right breast, which was less severely involved by the disease, the lymphatics were dilated and tortuous and there was good opacification of the afferent and efferent channels of an axillary lymph node. The lymphatics of the more severely involved left breast were poorly opacified and none of the opaque medium reached the axilla.

Venography was performed in 15 patients with lymphedema and there was no evidence of a significant abnormality in the involved upper or lower extremity.

The author believes that early in the course of filarial lymphedema the lymphatics become dilated. As the disease progresses they become narrow and occluded and collaterals are formed. He feels that stagnation and the accumulation of fluid rich in protein may cause hypertrophy of fibrous tissue. This leads to a permanent increase in the size of the part and explains the hard non-pitting edema seen in the late stages of filariasis.—*J. L. Williams, M.D.*

GENERAL

ALVAREZ-BORJA, ARTURO. Ellis-Van Creveld syndrome. *Pediatrics*, Aug., 1960, *26*, 301–309. (Address: Ahuachapan, El Salvador, Central America.)

The second recorded case of the Ellis-Van Creveld syndrome occurring in siblings is reported. The patients, brother and sister, presented with short stature, involving mainly the extremities, prominent abdomens, lumbar lordosis and genu valgum. Other physical characteristics were brachycephalic skull, lopped ears, abnormalities of the teeth, thinning of the upper lips in the midline, and supernumerary digits. No cardiac abnormalities were found. The laboratory tests were essentially negative.

The roentgen findings were basically as reported previously. There was generalized thickening and coarseness of the tubular bones, acceleration of maturation of the secondary centers and retardation of the primary centers of ossification. In the distal tibiae and fibulae there were areas of osteosclerosis intermingled with rarefactions. The heads of the radii and proximal ulnae were enlarged with narrowing of the opposite ends. Peaking of the proximal ends of the tibiae, described by Caffey as pathognomonic, was well illustrated. Curvature of the humeri was present. The thoraces were narrow with horizontal clavicles. The third cuneiforms were absent bilaterally in both cases. The articular spaces were normal.

The microscopic findings consisted of decreased osteoid formation and loss of columnar arrangement of the chondrocytes. The intrinsic mechanism responsible is not known.

The syndrome is apparently hereditary, transmitted recessively.—*Barry Gerald, M.D.*

GORSON, ROBERT OWEN, LIEBERMAN, JESSE, and GREEN, MARVIN. A limited survey of radiation exposure from medical fluoroscopes. *Radiology*, Dec., 1959, *73*, 898–910. (Address: R. O. Gorson, Jefferson Medical College Hospital, Philadelphia 7, Pa.)

The authors present the results of a comprehensive survey of the radiation characteristics of 81 medical fluoroscopes. Twenty-two units were located in eight hospitals and four city clinics while the remaining 59 were in the offices of physicians in private practice. The data were obtained by questionnaire, physical inspection, measurement of radiation characteristics, and determination of radiation exposure to the physician.

The radiation measurements were made with the field size of the primary beam adjusted to 10×10 cm. at the panel surface or table top. The half value layer was determined by the inferential method whereby aluminum caps of varying thickness were machined to fit over the sensitive volume of a Victoreen 25 r condenser ionization chamber. A ratio of the chamber reading with the cap on to the reading with the cap off was calibrated as half value layer function. The half value layer calibration curve for aluminum caps as used here is independent of tube potential. All readings were taken with the chamber in the center of the field, in contact with the panel surface, and corrected to an exposure dose rate at the panel surface according to the inverse square law. Scattered and leakage radiation at various positions around the fluoroscope and in front of the fluorescent screen was measured by ionization rate meters. This information was used to calculate a "stray radiation index" (SRI) to allow comparison for machines and correlation with film badge readings. Fifty-three physicians were provided with two film badges each, with instructions

to wear one badge on the right arm and one on the left shoulder.

Data from the physical inspection of the fluoroscopic units disclosed wide variation from recommended safety precautions. About 40 per cent of the horizontal units and 97 per cent of the vertical units had target-to-panel distances measured or estimated to be less than 18 inches, the minimum distance recommended by the National Committee on Radiation Protection and Measurement (NCRPM). In the majority of machines, certain safety features for the fluoroscopist were absent in that the machine could be energized with the screen out of position, and, at maximal shutter openings, the recommended one-quarter inch of unilluminated screen was absent. Many fluoroscopes did not have metal tube housings or shockproof cables.

The results of radiation measurement likewise revealed a wide variation. One-half of all the fluoroscopes failed to meet the requirement that the exposure dose rate at the table top or panel surface not exceed 10 r per minute for routine fluoroscopy. Using a minimum acceptable half value layer of 2.5 mm. of aluminum, about 30 per cent of the fluoroscopes owned by hospitals and radiologists and 80 per cent of the units owned by nonradiologists failed to meet this requirement. The stray radiation index (SRI) was higher for fluoroscopes owned by hospitals and radiologists. This is undoubtedly due to the higher tube potentials and half value layer used by these groups. Only 17 per cent of the fluoroscopes failed to meet the maximum screen transmission requirement of 20 mr per hour. The film badge readings were low, with an average value of about 5 mr per week for the right arm and 2 mr per week for the left shoulder.

The authors recommend the following standards, as used in their survey, to assure a reasonable degree of inherent radiation safety: half value layer of at least 2.5 mm. of aluminum; table top or panel exposure dose rate of 10 r per minute or less; exposure at the screen not to exceed 20 mr per hour; SRI not to exceed 50 mr per hour; and no part of the primary beam should extend beyond the primary roentgen-ray barrier. Probably not more than a half-dozen units would have met all the criteria but fully 90 per cent could be made acceptable by adjustments in filtration, shutter opening, shielding, or milliamperage.

The basic principles of good fluoroscopic technique are discussed. The authors conclude that improvement in standards of fluoroscopic practice will continue to evolve primarily through the educational efforts of medical groups and institutions.—*Edward B. Best, M.D.*

RADIATION THERAPY

Scheidegger, S. Spätschädigung des Rückenmarkes bei Röntgenbestrahlung. (Late damage to the spinal cord after roentgen therapy.) *Radiol. clin.*, Mar., 1960, *29*, 65–70. (From: Pathologisch-anatomisches Institut der Universität, Basel, Switzerland.)

A case report is presented of late damage to the cervical spinal cord following intensive roentgen treatment of a squamous cell carcinoma of the pyriform fossa. The patient was a known hypertensive when he underwent treatment. Soon after completion of radiation therapy, he developed ataxia and sensory disturbances. He expired two years after treatment with the cause of death being a cerebrovascular accident. Autopsy findings showed extensive hyalinization of the walls of the vessels within the area of irradiation and a diffuse demyelination with ganglion cell degeneration of the lateral columns.

It is assumed that hyaline degeneration of the vessels was present at the beginning of the radiation treatment due to the hypertensive disease. Roentgen treatment aggravated this condition considerably, as the already damaged vascular walls seem to be more sensitive to the effect of irradiation.—*Eckart Schackow, M.D.*

Decker, K., and Lauter, H. The results of treatment of hypophyseal tumours; a retrospective survey. *German Med. Monthly*, Aug., 1960, *5*, 265–267. (Address: K. Decker, Universitäts-Nervenklinik, Nussbaumstr. 7, Munich 15, Germany.)

One hundred twenty-four cases of hypophyseal tumors are discussed. Of these 103 were followed for a period of two to twenty-five years. Approximately one-third of these had features of acromegaly. Surgery was performed on 50 per cent of the cases while roentgen therapy was the initial treatment in the other 50 per cent. Surgery was performed by the transfrontal approach. Roentgen therapy was done with Kohler's apparatus. The field size was 3 or 4 cm., according to tumor size. The submaxillary field proved especially useful in a few acromegalics because it gave good dosage distribution with decreased irradiation of cranial nerves. This apparently was only possible because of the acromegalic physiognomy. Of the operated cases, 17 were eosinophile adenomas and 56 were chromophobe adenomas. The operative mortality was 16.4 per cent.

The rate of recurrence was low for both roentgen and surgically treated groups. Of 103 patients, 72 are still alive and 52 of these are able to work and are considered cured; the condition of the remaining 20 patients is unsatisfactory with endocrine and psychiatric disturbances being mainly responsible for this. The hormonal upset is usually adrenal cortical insufficiency with symptoms of Addison's disease. Of 39 patients treated with roentgen rays, 20 are healthy and able to work while 12 needed further surgery and irradiation.

The authors call attention to the extrasellar exten-

sion of these tumors as a factor in increased surgical mortality as well as in the reduced efficacy of roentgen therapy. The subsequent course of the tumor seems to bear little relation to whether therapy was by surgery or roentgen ray. Contraindications to roentgen therapy include suprasellar damage and rapid deterioration of vision.—*David Morse, M.D.*

del Regato, J. A., and Sala, J. M. The treatment of carcinoma of the lower lip. *Radiology*, Dec., 1959, *73*, 839–844. (Address: J. A. del Regato, 2200 N. Cascade Ave., Colorado Springs, Colo.)

The results of a study of 531 cases of carcinoma of the lower lip, treated between 1940 and 1953, are reported. In each case the diagnosis of carcinoma was confirmed by biopsy. The overwhelming majority of the tumors were well differentiated: 59 were of the verrucous type and 336 were Grade I carcinomas. There were 103 cases classified as Grade II and only 4 as Grade III. Grading was not done in 29 cases. Only 33 (6 per cent) of the 531 cases in this series presented metastases on admission. In an additional 39 patients, metastases subsequently developed.

Most of the small lesions measuring less than 2 cm. in diameter and without metastases were treated by simple V excision. An absolute three year survival of 81 per cent is reported for this group. Almost identical results were obtained for this size lesion by curie therapy and roentgen therapy.

Lesions 2 to 12 cm. in diameter were treated in most instances by roentgen therapy. The absolute three year survival averaged 73 per cent, being about the same for all therapeutic procedures. Roentgen therapy is regarded as the treatment of choice in the majority of lesions of moderate or large size in the absence of metastases. Surgical removal of larger lesions usually requires cheiloplasty, and the functional and esthetic results may be less satisfactory than those of roentgen therapy. Resection of the primary lesion may be chosen to expedite the surgical treatment of a metastasis or to take care of recurrent carcinoma. Radical neck dissection is recommended as the treatment of choice for cervical metastases. Prophylactic neck dissection is not advocated as a routine procedure.

A total of 103 additional patients were admitted with recurrent carcinomas of the lower lip following treatment elsewhere. In this group there were 26 (25 per cent) with metastases, a proportion four times as great as that observed in those who had received no previous treatment. The curability of this group was inferior to the other group with all methods of treatment.—*Arno W. Sommer, M.D.*

Buschke, Franz, and Galante, Maurice. Radical preoperative roentgen therapy in primarily inoperable advanced cancers of the head and neck. *Radiology*, Dec., 1959, *73*, 845–848. (Address: F. Buschke, University of California Medical Center, San Francisco 22, Calif.)

Surgery and radiation therapy are not competitive or mutually exclusive. The well-planned utilization of both forms of treatment can be of great help in the management of properly selected cases. Close cooperation between surgeon and radiotherapist in planning prior to treatment and throughout the entire treatment course is necessary. The most significant progress in radiation therapy during recent years has been due to longer protraction and radiation of shorter wave length. It is possible to introduce high cancerocidal doses with preservation of the vasculo-connective tissues by the judicious use of these two modalities.

The authors selected a number of patients with advanced epitheliomas of the oral cavity and oral pharynx for a planned combination of radical surgery with radical preoperative irradiation. The lesions represented differentiated epitheliomas of pillar, palate, floor of the mouth and gingiva, of a type that can be expected to infiltrate locally or to remain limited to the regional lymphatic areas for a long time, but too extensive for complete removal by primary surgery. The aim was to carry the dose high enough for control of the peripheral portion of the tumor but without attempting to sterilize the more resistant central portion. Fields were large enough to include the peripheral portion of the disease. Radiation therapy was given at one million volts (3.2 mm. Pb half value layer) through a single field. The dose varied between 6,000 and 8,000 r (skin) in thirty-two to fifty-nine days, for a minimal tumor dose (calculated at the most distant edge of demonstrable involvement) of 4,100 to 6,500 r. No attempt was made to include the lymph nodes, palpable or not, unless they happened to be in the field used for irradiation of the primary tumor.

Surgery was done from one to five and one-half months after completion of irradiation. The interval should not exceed two to three months because of the progressive vascular and fibrotic changes. A combined operative procedure was employed whereby the primary lesion was removed *en bloc* with the cervical lymph nodes. Between February, 1957 and February, 1958, 9 patients were accepted for the planned procedure. In 6 instances the treatment was completed as originally intended. In 2 patients the tumor regression was sufficient to warrant anticipation of possible control by irradiation alone and surgery was abandoned. Surgery was abandoned in 1 patient with carcinoma of the tonsil because true tonsillar carcinoma is not considered suitable for this type of operation.

In spite of the heavy preoperative irradiation, there were no surgical complications beyond those associated with this type of surgery when done initially. No fistulas occurred. No conclusions are possible

at this time regarding the final results, but it is emphasized that the risk of surgery in heavily irradiated tissue is not prohibitive.—*Arno W. Sommer, M.D.*

Baclesse, F., Ennuyer, A., and Cheguillaume, J. Est-on autorisé a pratiquer une tumorectomie simple suivie de radiothérapie en cas de tumeur mammaire? (Is one justified to perform a simple tumorectomy followed by roentgen therapy in cases of breast cancer?) *J. de radiol., d'électrol. et de méd. nucléaire*, Mar.–April, 1960, *41*, 137–139. (From: Fondation Curie, Paris, France.)

From 1937 to 1953, at the Curie Foundation, 100 patients with breast carcinoma in Stage I and II underwent simple local tumor excision (tumorectomy) followed by roentgen therapy. The patients so treated had refused radical surgery, or had undergone surgery for an expected benign tumor which at histologic examination proved to be malignant, or were simply referred for this treatment by the surgeon. In all cases, surgery consisted of a simple resection of the tumor, and not the MacWhirter type of mastectomy.

According to the authors, roentgen therapy must be started at the earliest possible time, and not later than the day the sutures are removed. The technique includes the use of 6 or 7 ports so distributed as to deliver a sufficient dose both to the mammary gland and lymph nodes. Minimum doses given were in the range of 4,000 r to the skin, 6,500 r at the tumor site and 6,000 r to the axillary lymph nodes. Each port was usually given 4,000 r with an additional 1,000 to 1,500 r delivered over a small area at the tumor site. The irradiation was protracted over a period of two and one half to three months.

At the end of a five year period, 64 per cent of all the cases so treated were alive and free of cancer, while at the end of ten years 50 per cent, that is, 11 out of 22 cases, apparently were cured. Of the histologically classified Grade I cases, 92 per cent were free of cancer after five years, but with Grades II, III and IV the percentage fell to 53 per cent, showing the importance of the histology on the outcome of the treatment. The age of the patient when the cancer is diagnosed is a paramount factor, since patients under thirty-five years of age have the worst prognosis.

Local recurrences have developed and two were encountered after eight and ten years in the Stage II group. Of the 10 cases with recurrences, 4 had undergone surgery and had survived five years or more, bringing the total five year survival rate to 68 per cent.

Objections to this treatment of breast carcinoma are numerous and well known. However, this technique is not proposed for indiscriminate use in all cases. It is to be considered as an exception and is to be used when patients refuse radical surgery. In Stage I and II cases, and with patients over thirty-five years of age, this technique yields results as good as those obtained by other methods. The present technique also confirms the efficacy of roentgen therapy in the treatment of the breast tumor and the lymphatic extensions. These results corroborate those obtained by using roentgen therapy exclusively (Baclesse) and by MacWhirter's technique of simple mastectomy followed by roentgen therapy.—*Robert L'Abbe, M.D.*

Berger, Simon M., Ingleby, Helen, and Gershon-Cohen, J. Roentgenography and biopsy in mammary cancer. *Radiology*, Dec., 1959, *73*, 891–895. (Address: S. M. Berger, Albert Einstein Medical Center, Northern Division, Philadelphia 41, Pa.)

The authors believe that roentgenography of the breast can achieve a high level of accuracy in the diagnosis of a benign or malignant lesion of the breast. Confirmed studies of a large number of patients have shown that where the findings clearly indicate either a benign or malignant tumor, accuracy is better than 95 per cent. With less definitive roentgenographic findings, particularly in adolescents and some young adults, the diagnosis is less reliable. This occurs in approximately 10 per cent of all breast examinations.

Malignant lesions as small as 0.5 cm. in diameter have been diagnosed and many (48) entirely unsuspected or asymptomatic cancers have been found. The incidence of axillary lymph node metastases in these was only 13 per cent in contrast to 64 per cent in cases diagnosed at surgery.

The cardinal roentgen criteria of carcinoma of the breast are: (1) the presence of an irregular or spiculated opacity, usually seen in scirrhous carcinoma; (2) a rounded opacity with localized notching or infiltration as in medullary or adenopapillary types of carcinoma; and (3) needle-point calcification arranged in clumps, sometimes linearly and at other times widely scattered, frequently noted in duct carcinoma.—*D. N. Dysart, M.D.*

Bloedorn, Fernando G., and Cowley, R. Adams. Irradiation and surgery in the treatment of bronchogenic carcinoma. *Surg., Gynec. & Obst.*, Aug., 1960, *111*, 141–146. (From: Division of Radiotherapy, Department of Radiology, and Division of Thoracic Surgery, Department of Surgery, University of Maryland Hospital, Baltimore, Md.)

This is an encouraging report on the results of a combined method of therapy for bronchogenic carcinoma employing preoperative cobalt 60 teletherapy followed by pneumonectomy. Out of a series of 26 patients for whom combined irradiation-operation treatment was planned, there was a survival rate of 62 per cent with survival times ranging from ten months to forty-four months. Fifty per cent of the group

which received combined irradiation-operation were considered inoperable. Of the 18 who received the combined treatment, 13 are alive and without evidence of disease to the date of this report.

Irradiation was delivered by cobalt 60 supervoltage apparatus achieving a tumor dosage of between 5,500 to 6,000 r. After a two month postirradiation waiting period to allow sufficient time for the acute tissue reaction to subside, a pneumonectomy was performed.

The following interesting facts were noted: (1) a high resectability rate following cobalt 60 therapy; (2) a low incidence of mediastinal lymph node metastases after irradiation; (3) a lowered incidence of distant metastases with this combined method of treatment; and (4) a lack of complications attributable to this combined procedure.—*B. Loitman, M.D.*

FLEISCHER, NORMAN and WALKER, RICHARD. Gastric carcinoma following successful therapy for primary gastric lymphosarcoma. *South. M. J.*, Aug., 1960, *53*, 965–968. (From: Divison of Pathology and Microbiology, University of Tennessee College of Medicine, and City of Memphis Hospitals, Memphis, Tenn.)

The authors report a case of primary gastric lymphosarcoma treated by subtotal gastrectomy and radiation therapy. This was followed in five years by a gastric carcinoma in the residual pouch with regional metastases. Both tumors were confirmed on tissue biopsy. The apparent cure of the previous lymphosarcoma was substantiated on autopsy.

The possible factors leading to the development of the gastric carcinoma are discussed.—*B. Loitman, M.D.*

KENT, STANLEY W., and MCKAY, DONALD G. Primary cancer of the ovary; an analysis of 349 cases. *Am. J. Obst. & Gynec.*, Sept., 1960, *80*, 430–438. (Address: S. W. Kent, 42 Deerings St., Portland, Me.)

This study consists of an analysis of 349 women with previously untreated primary cancer of the ovary seen at the Free Hospital for Women, Brookline, Massachusetts, from 1904 through 1952. The follow-up period was at least five years. The microscopic grading of the tumors was done according to criteria established by Allen and Hertig. The clinical staging is the standard one proposed by Munnel and Taylor.

The most common presenting symptoms were pain, abdominal distention and abnormal uterine bleeding. The five year salvage related to duration of symptoms for a period over six months is 42 per cent and 34 per cent when present for a lesser period of time. This probably indicates that the rapidly growing tumors produce symptoms earlier than those with slower growth. Ovarian cancer is less malignant in younger women and most frequently is found in the forty to fifty-nine year age group.

The serous cystadenocarcinomas were most frequently encountered; 31.3 per cent of them were Grade III, while only 7.1 per cent of pseudomucinous cystadenocarcinomas were so graded. Of patients with Grade I carcinoma, 65 per cent survived five years while only 10.4 per cent with Grade III lived that long. These statistics confirm the prognostic value of grading. The five year survival according to stage is: Stage I, 53.4 per cent; Stage II, 59 per cent; Stage III, 40 per cent; and Stage IV, 10 per cent.

Immediate postoperative irradiation was given to the pelvis and low abdomen of 154 patients, while 173 received no irradiation. The five year survival rate in the former group was 45.5 per cent and in the latter, 32.9 per cent. The significance of the grade of the tumor related to the radiation response was most marked in Grade III. In this grade, survival following surgery alone was 5.2 per cent compared to 18.8 per cent for roentgen irradiation and surgery. Stage I and III showed an increase in survival rate following irradiation, whereas Satge IV did not. Serous and undifferentiated cancers showed good radiation response, while pseudomucinous and granulosa cell tumors in this series did not. Conventional roentgen therapy employing 200 kv. with 0.5 mm. copper filtration and a target distance of 50 cm. was used. Portals of entry were 10×15 cm. or 15×15 cm. front and back, with usually two to the lower quadrants and one to the lower back. Exposures numbered 12 to 20. Total doses at skin level varied from 3,000 to 9,000 r. The dose to the midpelvic plane varied from 1,400 to 2,600 r.—*David Morse, M.D.*

TAKAHASHI, S., and MATSUDA, T. Axial transverse laminagraphy applied to rotational therapy. *Radiology*, Jan., 1960, *74*, 61–64. (Address: S. Takahashi, Hospital of the University of Nagoya, Showaku, Nagoya, Japan.)

Accurate knowledge of the size and location of a lesion is necessary for proper and effective use of rotational radiation therapy. Various methods of determining the external contour of the body cross section have been described but they do not indicate the location, shape and size of the lesion. Axial transverse laminagraphy eliminates this objection in that it provides a roentgen-ray image of a cross section showing both internal and external contour. Such laminagrams are usually made with the patient in the erect position. However, the cross section of the body changes in shape with a change to the supine position. This problem has been eliminated with the development of a unit for supine axial transverse laminagraphy.

The authors describe and illustrate their unit which was developed at the University of Nagoya,

Japan. Basically, it is a replica of the treatment table used in rotation therapy, around which a rotating frame was constructed. This frame, which rotates from 0 to 190°, serves as a mounting for the overhead tube and the synchronized rotating film holder which is beneath the patient. The essential features, therefore, are a rotating tube and film holder, and a stationary table. The central ray of the tube is set at an angle of 20° to the film surface; this produces a cross section considered to be 0.5 mm. thick. There is no distortion except for the magnification (×1.3).

A roentgenogram, or an axial transverse laminagram, made in this manner allows accurate positioning of the patient with the lesion at the center of rotation and permits calculation of the size of the radiation field and the depth dose.—*Edward B. Best, M.D.*

Kilár, Jaromír, and Bek, Václav. Zum Einfluss der Röntgen-Kontaktbehandlung der Hämangiome auf das wachsende Skelett. (The effect of contact roentgen therapy of hemangiomas on the growing skeleton.) *Strahlentherapie*, 1960, *111*, 561–573. (From: Radiologische Klinik der Universität Prag, Prag, Czechoslovakia.)

Of 708 children given roentgen treatment for hemangiomas or nevi between 1945 and 1953, 571 were re-examined in six to thirteen years. Between them they had had 726 hemangiomas and 34 nevi treated: 359 were of the head, 239 of the trunk, and 162 of the extremities. Cosmetic results of treatment were classified as unsatisfactory in 12 per cent of the patients followed. All patients were treated with a contact roentgen therapy unit at 50 kv., 2 ma., 2–4 cm. focal skin distance, and added filtration of 1 or 2.5 mm. Al, but, otherwise, treatment varied considerably. Doses of 300–600 r at intervals of two, four, and six weeks were changed gradually to 100–200 r several times a week and finally to daily doses of less than 100–200 r. Total dose per series of treatments was gradually reduced to 1,000–1,500 r. Forty-six per cent of the children received a single series of treatments, 38 per cent received two series, 12 per cent received three, and 4 per cent received more than four series.

Osseous changes occurred in 9 per cent of the patients; they varied from slight structural changes with shortening of 1–2 cm. of an extremity to orthopedic and functional abnormalities of considerable clinical importance. The frequency of some bone changes increased with the number of series of treatments administered, with the diameter of the area treated, and with decreasing age of the patient. Only 16.7 per cent of the osseous changes developed in children who were over a year old when treated; 59.8 per cent developed in children who were in their first six months.

As a result of this study, the authors (1) no longer treat telangiectatic nevi with roentgen radiation; (2) they believe contact roentgen therapy—and therapy with harder rays or radium—to be contraindicated for hemangiomas near superficial epiphyses, *e.g.*, digits, wrist, elbow, knee; (3) they have limited individual doses of contact roentgen therapy to a maximum of 100–150 r, the total dose in a series to 600–700 r, and the total treatment to no more than two series; and (4) they have employed roentgen examination in all follow-up studies because clinical inspection and comparison of external symmetry between treated and untreated extremities is insufficient to detect skeletal changes caused by treatment.—*Henry G. Moehring, M.D.*

Schwarzwald, Milan, and Vukadinovic, Gjorgje. Die Bedeutung der Elektroenzephalographie bei der Röntgenepilation der Kinderköpfe. (Electroencephalographic findings after roentgen epilation of children.) *Strahlentherapie*, 1960, *112*, 242–250. (From: Dermato-Venerologische Klinik der Medizinischen Fakultät Zagreb und Institut für medizinische Forschungen der Jugoslawischen Akademie der Wissenschaften und Kunst, Zagreb, Yugoslavia.)

Thirty-two boys and girls from four to ten years of age underwent roentgen epilation and had electroencephalography both before and, in most instances, seven days after therapy. Epilation was accomplished by treating each of five fields with 350 r (100 kv., 5 ma., 25 cm. focal skin distance, 0.5 mm. Al filter, half value layer, 1.2 mm. Al); when the patient's head was small, the central field received only 300–320 r.

This epilatory dose caused no change in the electroencephalographic tracings.—*Henry G. Moehring, M.D.*

RADIOISOTOPES

Cheitlin, Melvin D., Bernstein, Robert, and Langdon, Edward A. Varying responses to radioactive iodine (I^{131}) therapy in hyperthyroid patients. *Ann. Int. Med.*, Feb., 1960, *52*, 349–361. (Address: M. D. Cheitlin (MC), Walter Reed Army Hospital, Washington 12, D. C.)

A series of 14 patients, who were treated for hyperthyroidism with I^{131}, is presented, with the following types of responses: (1) euthyroidism after treatment with laboratory tests remaining abnormal; (2) euthyroidism resulting from a large total dose; (3) hyperthyroidism persisting after a large total dose; (4) eventual hypothyroidism after a large total dose; (5) abnormally low laboratory values after therapy with eventual return to normal; (6) temporary hypothyroidism, both clinically and by laboratory tests; and (7) hypothyroidism after a small dose of I^{131}.

These cases demonstrated the variability of response to treatment, the difficulty of dose calculation and the perplexing problem of predicting the ultimate outcome on the basis of short-term laboratory or clinical follow-up. The formula used to treat a majority of these patients was 100 μc I^{131} per gram of the thyroid gland.

The following factors were given to explain the varying responses to treatment: (1) the actual size and weight of the thyroid gland cannot be determined accurately; (2) the formula used assumes equal distribution of the radioactive iodine throughout the gland, which is seldom true; (3) the amount of radioactive iodine in the gland at any one time depends upon the uptake of the radioactive iodine and the time when it is secreted by the gland; this will vary in each individual; and (4) there is a variation in the response of the thyroid tissue to radiation from the radioactive iodine.

In deciding which patients will be re-treated, the clinical state of the patient is the best guide, since the physician cannot rely solely upon the thyroid uptake and protein bound iodine determinations following the first treatment.—*C. W. Ely, M.D.*

PERRYMAN, CHARLES R., PAVSEK, EDWARD J., and MCALLISTER, JOHN D. Clinical evaluation of radioactive chrome phosphate in the control of malignant pleural and ascitic effusions. *Radiology*, Dec., 1959, *73*, 865–870. (Address: C. R. Perryman, 1400 Locust St., Pittsburgh 19, Pa.)

The authors recommend radioactive chrome phosphate (P^{32}) as the agent of choice in preference to radiogold (Au^{198}), radioyttrium (Y^{90}), and nitrogen mustard in the treatment of malignant pleural and ascitic effusions. The advantage of chrome phosphate is that of a pure beta emitter with a relatively long half life. In addition, the material is noncytotoxic and therapeutically effective in doses of 5 to 10 mc. One of the nitrogen mustard derivatives, thiotepa, merits further clinical investigation.

Radioactive chrome phosphate was used in a total of 60 cases presenting either pleural or ascitic effusion. A dose of 5 mc was given in each case. Definite improvement was observed in 19 of the 38 cases of pleural effusion (50 per cent) and 10 of the 22 cases of ascitic effusion (45 per cent). Based on this experience, the authors now recommend a dose of 10 mc in the abdomen and 5 to 8 mc in the chest.—*Edward B. Best, M.D.*

ALBERT, SOLOMON N., ECCLESTON, H. N., JR., FUJITA, T., HUNTER, CHARLES H., and ALBERT, CHALOM A. Use of magnetic tape for recording radioactivity. *Radiology*, Dec., 1959, *73*, 923–926. (Address: S. N. Albert, Department of Anesthesiology, Washington Hospital Center, Washington 10, D. C.)

Radioactive isotopes are frequently used as tracer material for diagnostic purposes. Sometimes interpretation of disappearance curves is rendered difficult because of weak doses or inadequate settings of the rate meter as to scaling and time factors. To obviate loss of valuable data, commercial tape recorders have been employed to register disintegration impulses. This does not interfere with the routine counting system.

Details of wiring Nuclear-Chicago and Picker meters are given; a Norelco tape recorder was used. Tape recordings may be replayed by connecting to the input of a rate meter or scaler. By varying the replay speeds, poor quality curves can be improved for easier and better interpretation.

Three schematic drawings and three reproductions of cardiac output dilution curves using this system are included.—*J. C. Moore, M.D.*

HOLSTI, LARS R., and VOUTILAINEN, ANTERO. Über kombinierte Röntgen- und Radiophosphorbehandlung bei Mycosis fungoides. (The combined roentgen and radioactive phosphorus treatment of mycosis fungoides.) *Strahlentherapie*, 1960, *111*, 139–148. (From: Strahlenklinik und Dermatologische Klinik der Universität, Helsinki, Finland.)

After treating 5 patients with mycosis fungoides by a combination of radioactive phosphorus and roentgen radiation, the authors permit themselves no far-reaching conclusions, but feel that:

(1) P^{32} is a useful therapeutic aid in treating patients with mycosis fungoides when the foci of disease are generalized, slowly growing, and not producing many or large tumors. It seems to have no effect in the rapidly growing, malignant forms, particularly when biopsy shows increased capillary formation in the superficial layers of the skin.

(2) P^{32} should be given at intervals of ten to fourteen days, by mouth or vein, in doses of 5–9 mc to a total of 27–29 mc. If it is effective and if the patient's blood is not seriously depressed by the therapy, this treatment can be repeated for recurrences.

(3) Local roentgen therapy was effective in all 5 patients; it should be used, following P^{32} therapy, to treat masses or local infiltrations.

Four of the 5 patients were benefited by P^{32} therapy (1 was improved dramatically). The fifth patient had extensive tumors and did not benefit. Radioactive phosphorus therapy caused anemia in 2 patients; 1 of these also developed a thrombocytopenia.—*Henry G. Moehring, M.D.*

HAWLICZEK, F., LANGNER, E., and SEEMANN, D. Zur Frage der zerebralen Radioangiographie. (Cerebral radioangiography.) *Strahlentherapie*, 1960, *111*, 280–285. (From: Sonderabteilung für Strahlentherapie des Krankenhauses der Stadt Wien Lainz und Neuro-

logische Abteilung des Altersheims der Stadt Wien Lainz, Austria.)

When 50 μc of radioiodine-tagged human serum albumen is injected into an antecubital vein, a scintillation counter over the confluence of the cerebral venous sinuses records a maximum count within 15–20 seconds in normals, 22–35 seconds in patients with obvious cerebral vascular disease, and 18–23 seconds in borderline cases. The curves for the normal subjects showed a rather abrupt rise and fall, while the curves for the definitely abnormal patients were much flatter.

The next step was the simultaneous recording of counts over the carotid artery and the cerebral venous confluence after injection of the radioactive serum albumen. The authors found that count-maxima occurred at longer intervals than those reported from serial angiography (8.5–13.0 seconds from the carotid injection until clearing of the cerebral vessels for the normals, and 12.5–16.0 seconds for the arteriosclerotic patients).

Five to ten minutes after administration of such vasodilators as ethylendiamine and purines, the time from antecubital injection to the maximum count at the venous confluence was lengthened. The authors assume that this indicates a greater cerebral vascular cross section, but they disclaim firm conclusions about the mechanism of this effect.—*Henry G. Moehring, M.D.*

MISCELLANEOUS

Stone, Robert S. The Gordon Richards Memorial Lecture 1960: Factors influencing maximum permissible doses of radiations. *J. Canad. A. Radiologists*, June, 1960, *11*, 26–34. (From: Department of Radiology and AEC Radiological Laboratory, University of California School of Medicine, San Francisco, Calif.)

In his Lecture Dr. Stone interprets the "permissible doses" set forth by the International Commission on Radiological Protection of which he is a member. There are different maximum permissible doses given for exposure of the total body, extremities, and separate organs, as well as for various groups in the community.

In 1934 the International X-ray and Radium Protection Commission meeting in Zurich determined from all known facts a "tolerance dose" of 0.2 r per day. In 1936 the Advisory Committee on X-ray and Radium Protection of the United States in National Bureau of Standards Handbook 20 lowered its "tolerance dose" to 0.1 r per day, because in the United States doses were measured in air as against skin dose measured on the Continent plus the fact that more penetrating rays of higher energy were being employed in the United States.

The early radiologists and physicists based their "tolerance dose" on the biologic measure of a skin erythema which is (1) a threshold type of reaction and (2) dose-rate dependent. Since with fractionation of dosage a skin erythema could be prevented, it was believed that daily small repeated doses were "tolerable."

After Muller demonstrated that roentgen rays produced gene mutational effects which were additive regardless of dose rate or fractionation, it was realized that this was a linear or non-threshold type of reaction. If this be true then there is no "tolerable" dose, and the setting of a maximal permissible dose becomes a matter of judgment when deciding upon an "acceptable risk." Three general effects, (1) life shortening, (2) leukemia induction, and (3) genetic effects, have important bearings on the permissible dose. Animal experimentation and statistical analyses in each of these categories find expert opinion on both sides of the question as to whether there is a threshold. Insofar as genetic effects are concerned, Dr. Stone opines we should assume that there is no threshold and keep gonadal exposure very low.

The sensitivity of the embryo and fetus with regard to malformations and malignancies in childhood presents for women in the reproductive age a special hazard. The International Commission on Radiological Protection has given recommendations of maximal permissible exposure in most circumstances except in medical radiology. Here they feel the physician should balance the good to be accomplished against any possible harm. All precaution should be taken to keep gonadal exposure to the lowest possible levels consistent with the patient's medical needs.—*B. Loitman, M.D.*

Seelentag, Walter, and Klotz, Erich. Die Strahlenbelastung der Bevölkerung durch Leuchtzifferblätter von Uhren. (Radiation exposure of the population from illuminated watch dials.) *Strahlentherapie*, 1959, *110*, 606–621. (From: Institut und Poliklinik für Physikalische Therapie und Röntgenologie der Universität München und Röntgenabteilung der Medizinischen Klinik der Städt. Krankenanstalten, Augsburg, Germany.)

Measurements on 38 different watches and clocks with illuminated dials demonstrated an average radium equivalent of 0.12 microgram for large alarm clocks, 0.08 microgram for travel alarm clocks, 0.03 microgram for small alarm clocks, and 0.04 microgram for wrist watches. Variations from the average were wide, up to five times the average value.

The radiation dose to the user of these timepieces averaged: 0.15 microroentgen per hour from the large alarm clocks, 0.10 microroentgen per hour for travel alarm clocks, 0.05 microroentgen per hour for small alarm clocks, and 0.6 microroentgen per hour for wrist watches. The source-user distance was assumed to be 1 m. for the alarm clocks and 30 cm.

for the wrist watches. The local dose to the forearm from a wrist watch averages 300 microroentgens per hour. These doses pose no threat of somatic damage to the user.

Sales personnel in a large watch store received a dose of up to 75 microroentgens per hour, an annual dose of 90 milliroentgens, approximately three-fourths of the natural background radiation level. Neither does this pose a threat of somatic radiation damage and, reckoned on the basis of the entire population, the genetic hazard also disappears.

The dose to the population from illuminated dials is estimated at 2.6 milliroentgens per person per year, about 2 per cent of the dose from natural background radiation, no genuine genetic hazard.

Whether this radiation dose is acceptable in return for whatever advantages illuminated dials present is beyond the scope of this investigation.—*Henry G. Moehring, M.D.*

Ritz, Victor H. Design of free-air ionization chambers for the soft x-ray region (20–100 kv.). *Radiology*, Dec., 1959, *73*, 911–922. (Address: National Bureau of Standards, Washington 25, D. C.)

The present study was undertaken to supplement the design of the standard free air ionization chambers (as described in the National Bureau of Standards Handbook 64), modified to measure ionization in the soft roentgen-ray region between 20 and 100 kv. Use of the standard free air chambers requires consideration of a number of factors. First, the roentgen is defined in terms of the ionization produced by the interaction of a roentgen-ray beam with a specified mass (volume) of dry air. This volume is influenced by three factors: the size of the diaphragm through which the beam enters, the length of the collector plate, and the electric field between the high voltage plate and grounded collector plate. The grounded lead box enclosure of the chamber causes distortion of this electric field however, and guard plates must be used to eliminate it. These plates themselves will also cause a certain amount of distortion, especially when they are close to the edge of the collector plate or when they are too widely spaced. Secondly, electrons produced by the interaction of the roentgen-ray beam and the air outside the collecting region will travel through the collecting area and produce ionization. Conversely, electrons produced within the collecting area will pass outside the area before producing ionization. Thus the proper design of the free air chamber requires a knowledge of the range of these primary electrons. Conditions may also exist where photons scattered from the primary beam reach the collecting area and produce ionization. This scattered photon contribution must be determined and subtracted from the total ionization measured by the chamber.

Also, a correction must be made for the attenuation of the roentgen-ray beam by the air between the diaphragm and the center of the collector. This correction becomes quite large when measuring soft roentgen rays. Decreasing the length of the air path between the diaphragm and collector plate will help nullify this factor but, in so doing, there is an increase in the distortion of the electric field caused by the guard strip system. As a result, the reduction of the air path distance is limited by its field distortion effect.

The present study deals with the measurement and correction of the above mentioned physical factors; namely, the distortion of the electric field in the collecting region by the guard strip system, the range of primary electrons and the scattered photon contribution, and other corrections such as air attenuation. The apparatus is described in detail and several schematic drawings are presented to show the experimental free air chamber which was used. The field distortion study is described and the results are recorded graphically. The method for determining primary electron losses is outlined and a series of graphs show the results at varying kv. energies and filtrations. Data are also given to show the scattered photon contribution at various voltages and at varying radii (cm.) from the roentgen-ray beam corrected to zero diameter. Reduction of the air path between the chamber diaphragm and the collector plate to a distance of 5 cm. was possible as a result of these studies. Values for air attenuation in this 5 cm. distance chamber were found to be about 0.15 per cent higher than similar values established by Day and Taylor using the standard free air chambers. Corrections for the humidity of the air may amount to plus 0.3 per cent in the soft roentgen-ray region under ordinary laboratory conditions. Methods of calculating this correction are found in Handbook 64.

The maximum errors in the factors investigated here may be summarized as follows: field distortion and errors in measuring the length of the collector ± 0.2 per cent, electron losses ± 0.1 per cent, scattered photon contribution ± 0.2 per cent and air attenuation ± 0.2 per cent. These values, combined with the estimates in Handbook 64 for uncertainties in the diaphragm area, charge measurement, etc. yield a probable limit of error of ± 0.5 per cent for the determination of exposure dose in r in the soft roentgen-ray region.—*Z. Petrany, M.D.*

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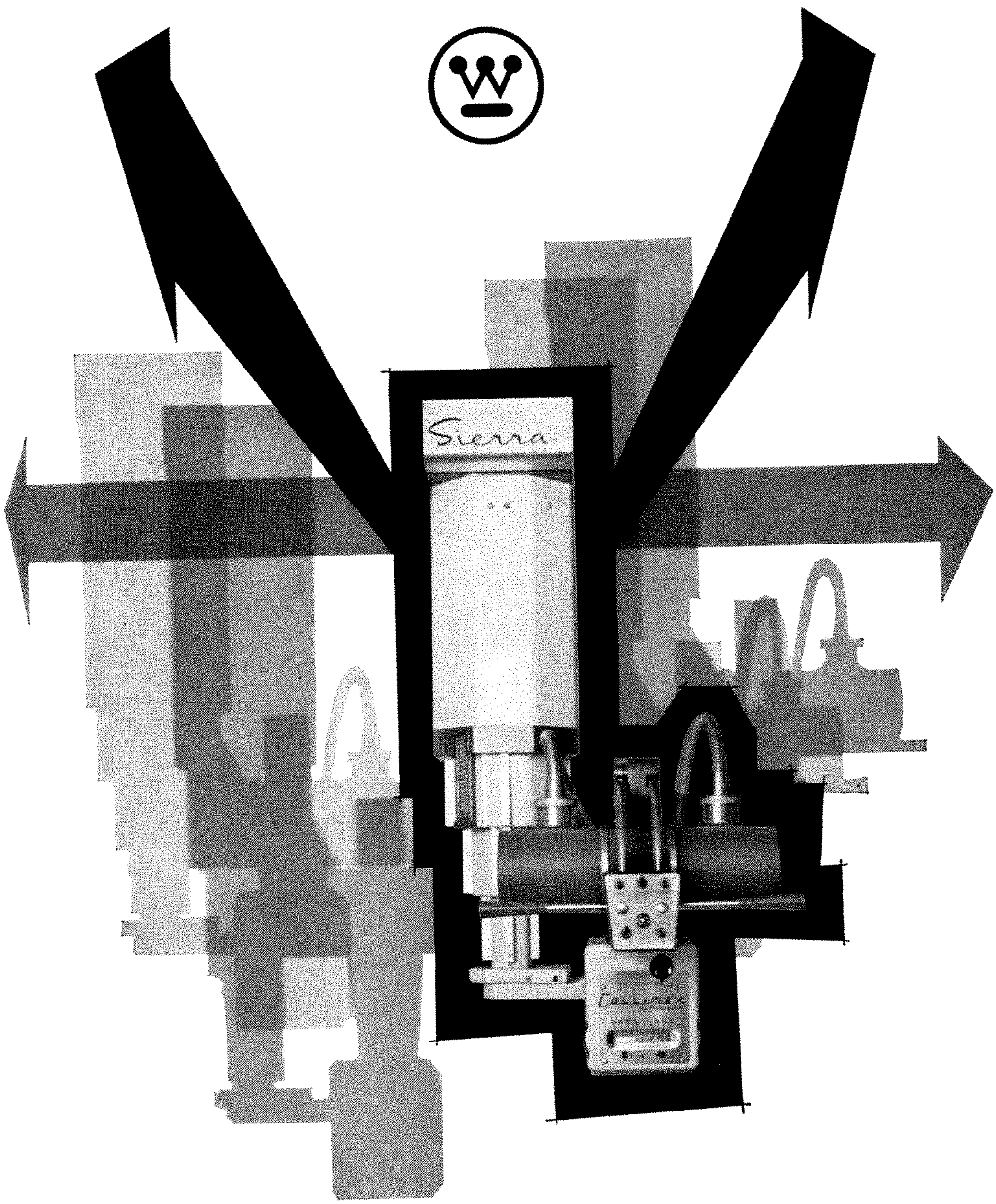

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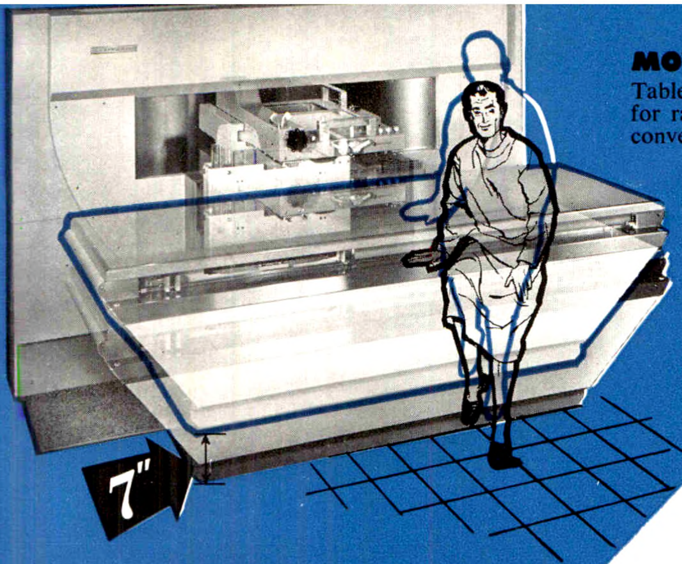
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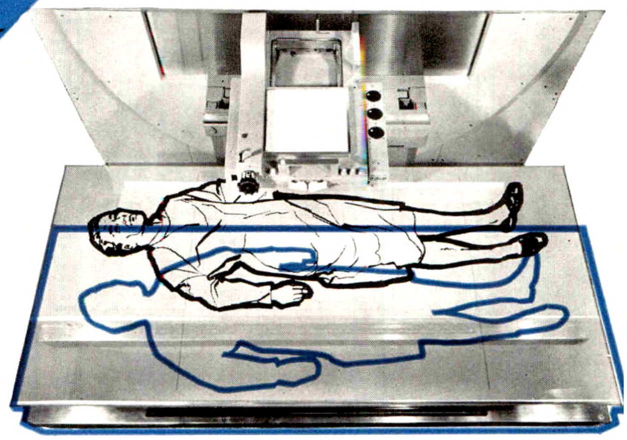

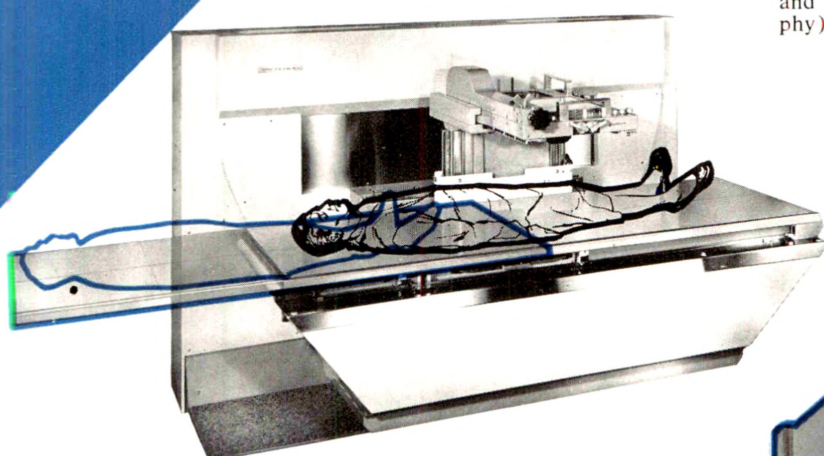

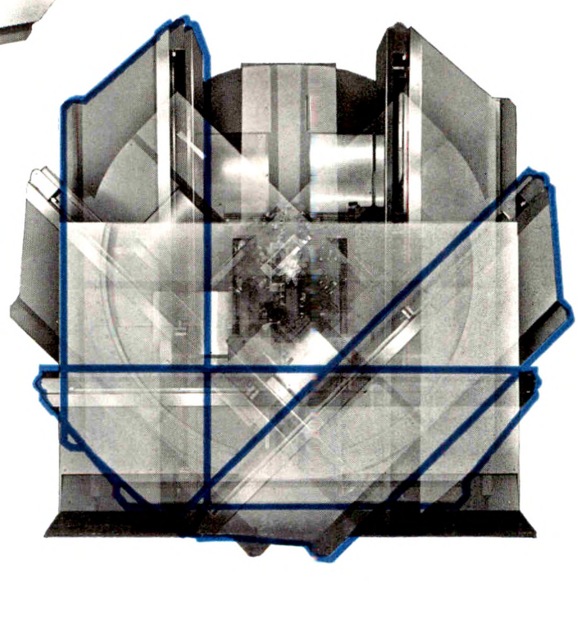

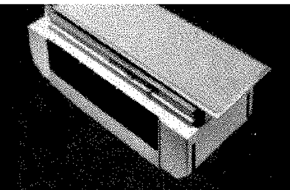

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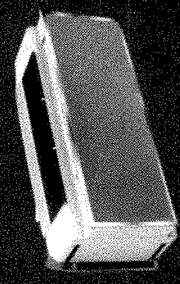

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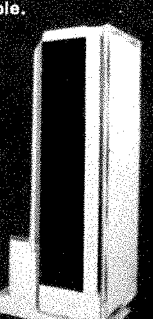

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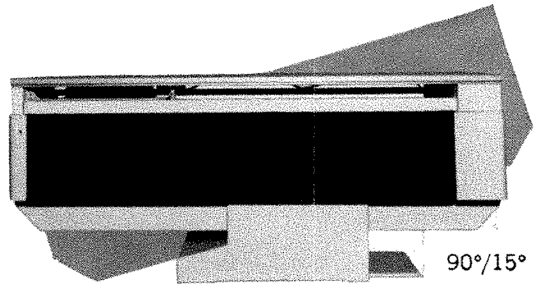

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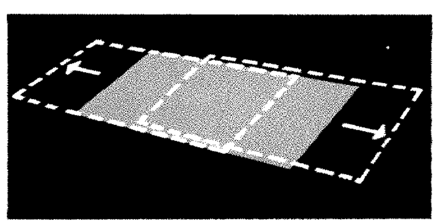

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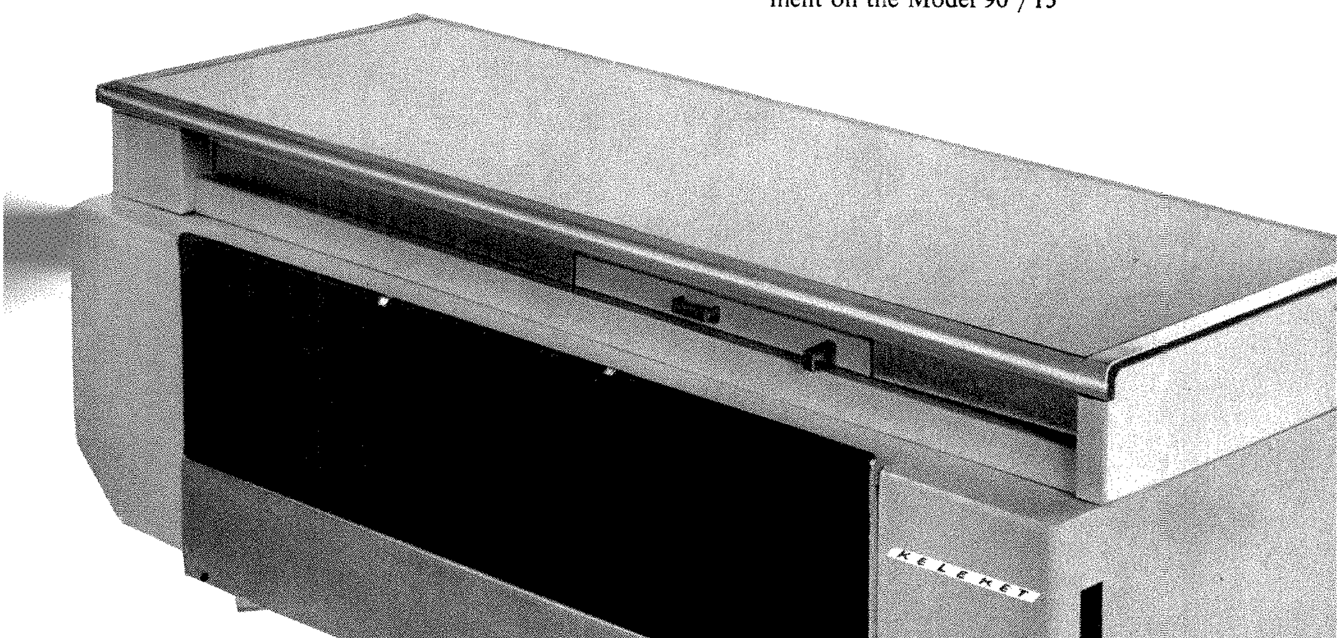

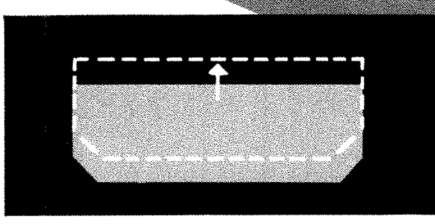

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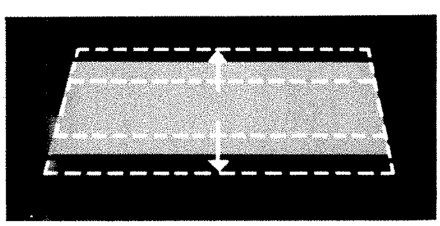

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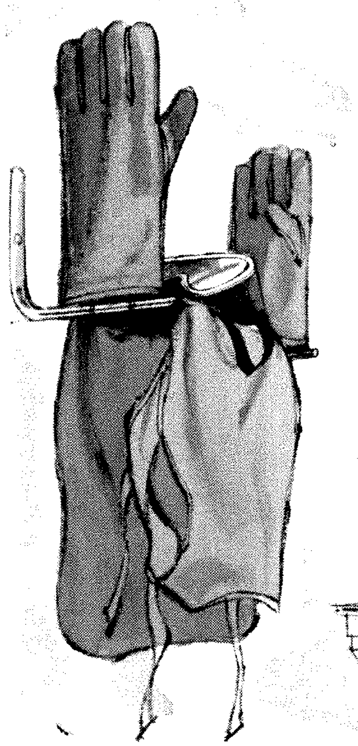

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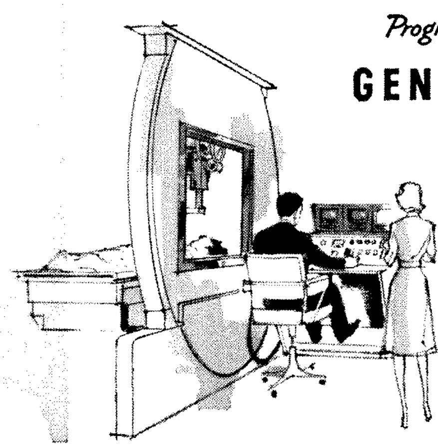

THEODORE R. MILLER, M.D.

THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 85 MARCH, 1961 No. 3

THE TRAINING OF THE CANCEROLOGIST*

THE PRESIDENT'S ADDRESS

By THEODORE R. MILLER, M.D.
NEW YORK, NEW YORK

IN GOING over the now well-established literature of the past presidents' addresses, I find that a great variety of subjects has been explored. The recent trend has been in topics of education and its various ramifications, but little has been said about the need for training oncologists. As this is a problem which poses some questions which might be solved by members of this society, I have chosen the subject, "The Training of the Cancerologist."

As a member of a group treating cancer in its many forms, I am impressed by the fact that approximately 70 per cent of the cases seen in our practice have had previous treatment. For example, of the last 100 patients with malignant melanoma, seen by us since July, 1958, 94 per cent had had previous treatment: 45 per cent had biopsy only and then were referred for therapy; 6 per cent had what, in the light of our present knowledge, could be considered adequate therapy but there were recurrences; and 42 per cent must be considered to have been improperly treated. The same is true of the soft tissue sarcoma patients referred to our service at the Memorial Hospital. On the gastric service, we are seeing an increasing number of persistent and recurrent gastric cancer cases which have been inadequately treated but which can still be salvaged or palliated by further surgery. In reviewing this material, one is struck by the fact that over half of all previously treated cases have been treated by general practitioners, the rest by general surgeons (some, Board certified) with no specific training in the treatment of cancer, or by radiologists who do only occasional therapy.

Cancer is one of the few diseases in which early diagnosis and prompt and proper treatment make the difference between life and death. The 42 per cent of the previously mentioned series, who must be considered as having been poorly treated, were obviously hopeless on first consultation with us and subsequently lost their lives. Some of these could have been saved by proper initial treatment. It is a truism that should require no elaboration that the physician treating cancer should have an intimate and extensive knowledge of the biologic nature and behavior of the disease. This point is illustrated by the following case histories.

* Presented at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960.

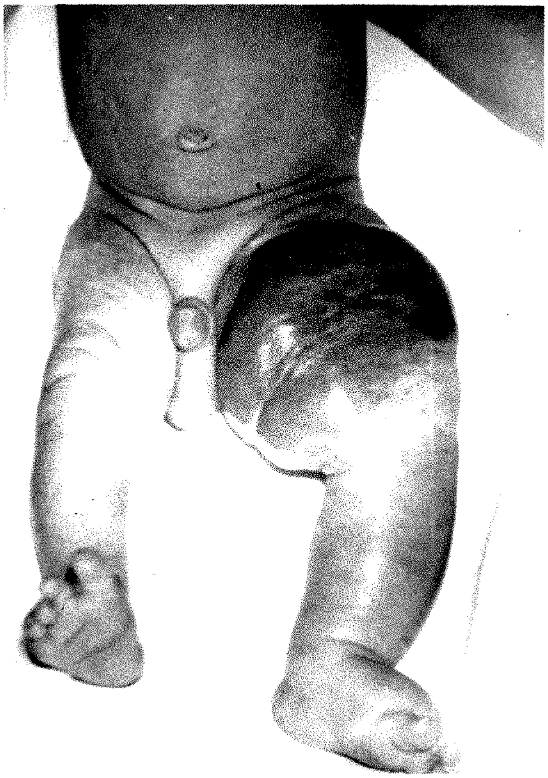

Fig. 1. Photograph showing the tumor of the left thigh of a one month old child.

Figure 1 shows a one-month old child with a large tumor of the left thigh. He had been seen by a radiotherapist who advised that he receive 4 treatments of 200 r each, given tangentially. A distinguished pediatric surgeon was called in consultation and recommended that amputation be done when the child recovered from the jaundice which had followed hormonal therapy and transfusion. Finally, he was seen by a trained tumor specialist, who, knowing the natural history of the disease (hypertrophic hemangioma), recommended that no therapy be given, as the tumor would naturally regress. Fortunately, the child's leg was not deformed nor amputated, and Figure 2 shows the child at the age of four with the leg returned almost to normal.

Figure 3 shows a similar case, first seen at the age of eight and one-half months. The child had been referred for amputation of what was thought to be a malignant tumor. Figure 4 shows the child at the age of fourteen months, and Figure 5 shows the child at the age of seven years. No treatment was given because of the knowledge that the tumor would regress spontaneously. There are reports in the literature of major amputations done for such tumors.

Cancer is a relatively rare disease, as evidenced by the fact that cancer patients occupy only 7 per cent of the beds in the average general hospital in the United States. This material is even further diluted by division among the various departments or specialists. It is easy to see why the general surgeon, the internist, gynecologist, pediatric surgeon, urologist, dermatologist, etc., trained in general or university hospitals which are not particularly interested in the treatment of tumors, can have little experience or knowledge of the biologic history of this protean disease. In contrast with this wide distribution of cancer cases,

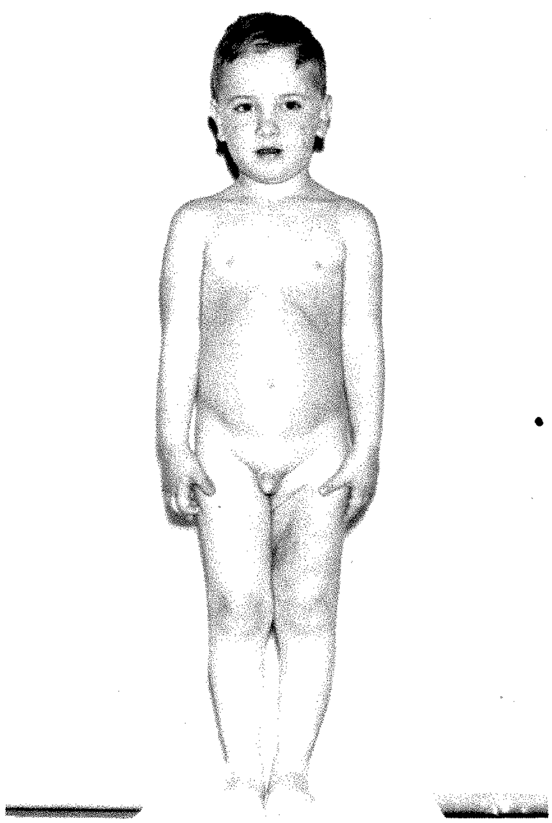

Fig. 2. Same child as in Figure 1 at the age of four.

Fig. 3. Photograph showing the arm of an eight and one-half month old child with hypertrophic hemangioma.

Fig. 4. Arm of the same child as in Figure 3 at the age of fourteen months.

Memorial Hospital admits 9 times as many as any general hospital twice its size in New York City. Thus, a resident spending three years at Memorial Hospital would have experience with cancer equal to twenty-seven years in a general hospital twice its size. Such concentrated training and material certainly should lead to a better understanding of the natural history of the disease and its proper treatment.

Fortunately, many of the patients who have had previous treatment are still salvageable. It is disturbing to note, however, the tendency for the highly trained specialist to apply to all forms of the disease the only method known to him. It is common for us to see the radiotherapist continuing treatment where viable cancer is evident along with radiation necrosis in the surrounding tissues. The surgical practice of taking multiple biopsies to determine operability, in the presence of an evident cancer, can only be condemned as showing a lack of knowledge of the na-

Fig. 5. Arm of the same child as in Figures 3 and 4 at the age of seven years.

Fig. 6. Large retroperitoneal liposarcoma.

ture of the disease. The so-called "second look" principle indicates that the first look was obviously inadequate and that the approach to the extirpation of the cancer had been timid. The principle of plucking nodes from a cancer-bearing area as one might pluck raisins from a bun shows complete disregard of the well-established procedure of block dissection. The extreme philosophies of the inexperienced, which are based on the behavior of cancer at either end of the normal distribution curve, lead either to the nihilistic attitude that all cancer is hopeless, or to the equally unrealistic position that the cancer patient can be salvaged by almost any minor procedure. The constant reiteration of these fallacious principles in the literature and in training centers has done the cancer patient a great disservice.

The cancerologist should have a knowledge of the standard procedures in cancer surgery and a familiarity with the effects of ionizing radiations, as well as an understanding of the chemotherapeutic and hormonal approaches. The great significance of the biologic approach to cancer therapy is embodied in this principle. Although the usual feeling is that such training would require the powers of the Trinity, practical teaching and research in cancer must be a single discipline. In which field the trainee chooses to practice is an unrelated problem. The following case histories indicate that knowledge of the basic principles of all disciplines is not beyond the comprehension of the ordinary mortal.

Figure 6 shows the operative specimen removed from a young woman, aged twenty-five, who was first seen in October, 1951. She had a huge tumor in the left upper quadrant of the abdomen. She had been under the care of her physician because of discomfort of ten months' duration. A nodule had been removed from her left neck and a diagnosis of metastatic liposarcoma had been made. A roentgenogram of the chest on admission showed a mediastinal mass. The abdominal mass was removed in November, 1951. The patient was then given radiation therapy, using supervoltage, to the mediastinum and the bed of the excised tumor. The neck lymph nodes were treated with orthovoltage, as was a mass in the left popliteal space. A node appeared in the right carotid lymph node region and was treated with orthovoltage. In 1953, further disease appeared in the right neck and in the upper mediastinum. In December, 1953, an exploratory laparotomy was done because of symptoms of intestinal obstruction, and Figure 7 shows the operative specimens of omentum, a segment of the small bowel and a segment of the transverse colon which were removed because of involvement with metastatic liposarcoma. In April, 1955, another area of disease was noted in the right neck and treated with radiation therapy. Since this time, the patient has remained well with no

evidence of any activity of the disease, a matter of five years. I feel certain that such successful combinations of radiation therapy and surgery are not uncommon in the experience of the members of this Society. This case illustrates the value of an over-all knowledge of both modalities of treatment, and their application by the same individual.

Figure 8 shows a male, aged fifty, with a sarcoma of the presternal region, who had been operated on eleven times by a surgeon in an effort to eradicate a fibrosarcoma. He finally gave up at this point, and referred the patient to our institution for treatment. The patient was still operable and possibly curable. Figure 9 shows the operative specimen. The patient is now well, approximately ten months, without evidence of recurrence.

The modern trend of the general hospital and the university hospital toward avoiding concentration of cancer patients and treating them on the various specialty services is the fault of the administrative professors who are the planners of graduate

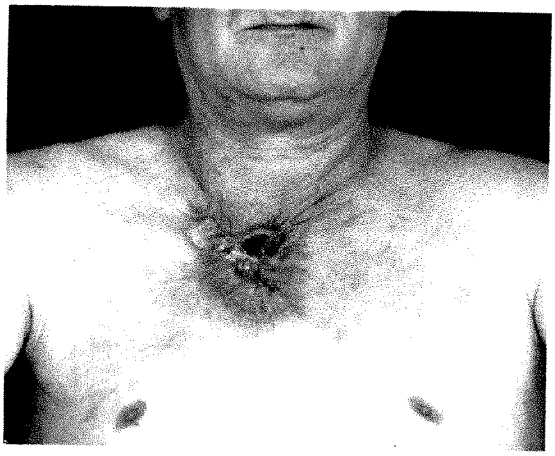

FIG. 8. Photograph showing a sarcoma of the presternal region in a fifty year old male.

medical education. The tendency for superspecialism to take over training, with the resultant isolation of specialties, is aided and abetted by the rigidity of the qualifying boards, which strive to narrow the

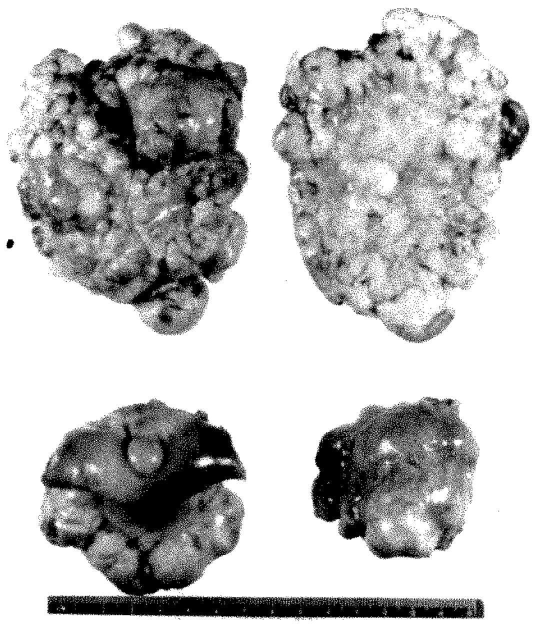

FIG. 7. Operative specimens of omentum, small bowel and transverse colon showing recurrent liposarcoma.

FIG. 9. Operative specimen from the patient shown in Figure 8.

scope of training and, consequently, experience in other fields. The unique character of the American Radium Society, in reality the oldest national scientific society primarily interested in the treatment of cancer, places it in the position to influence the trend of postgraduate medical education. Of the 342 members from the United States, 155 hold academic rank. There are 67 members certified by the Board of Surgery, 163 members certified by the Board of Radiology, and 24 members certified by the Board of Obstetrics and Gynecology. There are a number of members certified by the Boards of Internal Medicine, Dermatology and Syphilology, Urology, and Pediatrics. The membership includes physicists, dentists, and even a veterinarian. With this broad representation among the various certifying boards and the academic rank held by so many members, it is the most vital function of this Society, through its members, to train men in the broad knowledge of the disease and, therefore, in better understanding and treatment of the cancer patient.

139 East 36th Street
New York 16, New York

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THE PLACE OF INTERSTITIAL GAMMA-RAY EMITTERS IN RADIATION THERAPY*

INDICATIONS—TECHNIQUE—EXAMPLES

By FERNANDO G. BLOEDORN, M.D., CARLO A. CUCCIA, M.D., *and* RAUL MERCADO, Jr., M.D.
BALTIMORE, MARYLAND

THE progress of radiation therapy in the last decade has been characterized by technical developments: the use of supervoltage, isotopes, moving field techniques and the application of more scientific dosimetry. At the same time very little has been done to develop further the techniques of interstitial irradiation which have proved to be so efficient in the treatment of a number of malignancies. The tendency in most radiation therapy centers is to abandon the use of radium in favor of external beam therapy even in cases where its efficiency has been proved by the good results obtained. Very few significant works in interstitial therapy have been published in recent years. The general tendency seems to be to exaggerate the disadvantages of the procedure rather than to look for improvement.

In spite of all the advances made in modern external beam therapy, there is a group of conditions which still is best benefitted by interstitial therapy, providing the indications, performance and dosimetry are properly considered. Undoubtedly, if more therapists become interested in developing the procedure, many of the objectionable features can be overcome or minimized. None of the objections against this technique of treatment are insurmountable if enough effort and ingenuity are put into the endeavor. More emphasis should be placed on the benefits of interstitial therapy and all its possible indications in order to exploit its therapeutic potentiality; only after this trial is a fair comparison with other means of therapy possible.

If one can avoid the haphazard procedures based only on empiricism, but still used today by many therapists, the whole field of interstitial therapy could be further developed on a more scientific basis with wider indications, less risk, and better results.

In recent years there have been several attempts to replace radium as a source of gamma rays for interstitial irradiation. Co^{60}, Ce^{137}, Au^{198}, Ta^{182}, and Ir^{192} are the most important of these substitutes. As expected, there is no significant biologic difference between the radiation produced by these sources and that produced by radium. In some cases the malleability of the sources (tantalum wire and nylon threaded cobalt or iridium) offers some physical advantages from the standpoint of adaptability to the anatomic area to be implanted; in others, exposure from these sources is reduced to a minimum. They all have shorter half-life as compared with radium; therefore, added difficulties in dosimetry and source replacement are encountered. The flexibility of sources is not a desirable feature in all cases. We believe that rigid radium needles are better for the performance of a good implantation in the oral cavity, vulva, vagina, and in all cases where a cylindrical volume or any of the complex geometric pattern implants is indicated. The ideal approach is to have all types of sources available and to use the one most appropriate for each case. The flexible isotope sources are particularly suitable for extensive implants in flat, superficial areas where a large single plane is indicated, *i.e.*,

* From the Division of Radiotherapy, Department of Radiology, University Hospital, University of Maryland, Baltimore, Maryland.
Part of this work has been sponsored by the American Cancer Society.
Presented at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960.

chest wall recurrences from breast carcinoma, recurrences on the neck or groin after lymph node dissection, tumors of the skin, etc. The nylon threaded gamma-ray emitters offer the further advantages of reducing exposure to the operator.

As will be shown, in our institution an effort is being made to enlarge the indications for interstitial therapy by the use of complex geometric patterns of source distribution and by the implantation of bone and cartilage when involved by disease. Of course, these applications are possible only providing the proper distribution of sources and dosimetry are used. Uniformity and control of the dose are indispensable requirements if complications are to be avoided.

There exists another possible application of interstitial gamma therapy which is worth further exploration: the combination of external beam and interstitial therapy. There are many instances, especially in head and neck and some genital tumors, where combined therapy would present distinct advantages since the volume of normal tissues irradiated to very high dose levels would be reduced. With the increased use of 2 parallel opposing fields of supervoltage irradiation, the addition of interstitial treatment could reduce late radiation effects and avert complications in many cases.

This work represents the effort of our group to find the proper place for interstitial gamma therapy in the treatment of cancer. It is divided into four parts for better understanding.

PART I. GENERAL PRINCIPLES

A. ADVANTAGES OF RADIUM THERAPY (OR OTHER INTERSTITIAL GAMMA-RAY THERAPY)

Even with the increased use of supervoltage irradiation, interstitial gamma-ray therapy is the treatment of choice in many malignant tumors of the well-differentiated type which can be adequately covered by an implant. No other technique of irradiation will either offer the same advantages or yield the same results. Interstitial gamma-ray therapy is the only means of delivering supervoltage radiation where it is needed with maximum sparing of the normal tissues. The advantages can be categorized as follows:

1. *Accurate localization of the tumor and its extension.* Since all implantations should be performed under general anesthesia, an excellent opportunity is provided for examination by direct vision and palpation of the tumor.

2. *Irradiation is limited to the tumor bearing volume only* with proper adaptability of the shape. Irregular shapes of the irradiated volume may be devised to conform to the shape of the tumor; due to the sharp fall-off of the dose in interstitial therapy, the irradiation of the normal tissues is limited to a very short distance from the sources. No form of beam therapy can better spare the normal tissues.

3. *Supervoltage type of irradiation is used* with all its well-known advantages.

4. Due to the combination of (2) and (3) *a higher dose can be delivered safely* when required. This may be useful in the case of some of the well-differentiated squamous cell carcinomas and in most adenocarcinomas of the head and neck and genitalia. These tumors can be successfully treated by irradiation only by delivering a very high dose.

5. *Shorter treatment time.* This is a definite advantage in a busy department and generally represents less suffering and less economic stress to the patient.

Surprisingly enough, and in spite of these definite advantages, interstitial radium therapy has not had the acceptance that it deserves, probably because the disadvantages of the procedure have been overestimated. The most commonly mentioned disadvantages will be enumerated along with some of the possible ways of minimizing or avoiding them.

B. DISADVANTAGES OF RADIUM THERAPY

1. *Irradiation of personnel and operator.* This is no doubt the main drawback of the procedure. By using proper technique and protective devices in and out of the operating room, together with adequate sharing of

the exposure among members of the staff, the radiation can always be maintained below the maximum permissible level.

Whenever indicated, the use of nylon threaded gamma emitters (Henschke[3]) and empty shafts which are filled with the proper isotope when the implantation is finished (Suit) will further help in diminishing the exposure. It is always more justifiable to expose ourselves and our personnel (within tolerance limits) in the performance of a highly curative procedure rather than in one using some radioactive isotopes where the chances of curing a patient are practically nil. In our institution where the facilities are not ideal, we seldom exceed the permissible tolerance level of irradiation by the proper handling of radium, adequate technique, protective devices and the sharing of exposure among several operators.

2. *Lack of versatility—limited indications.* It is true that the indications for interstitial therapy are limited but with sufficient ingenuity and the use of complex patterns in the arrangement of the sources, the number of cases properly treated by interstitial therapy can be considerably augmented. The use of surgery for the implantation is also a way in which to further increase the adaptability of the procedure.

3. *It is a surgical procedure.* This requires admission to the hospital, general anesthesia, special skill of the therapist, etc. Except for the general anesthesia in poor risk patients, all other objections are unimportant if the results are justifiable.

4. *More difficult dosimetry.* In a well organized department of radiation therapy, this is not a disadvantage. In most cases the type of implants to be used can be calculated in a short time with proper training. Elaborate equipment or special training in mathematics or physics is not necessary.

5. *Danger of implanting in or near bone or cartilage.* This is not a valid objection as will be shown later. In order to obtain the best results from interstitial therapy, the care in planning the distribution of sources, the technique for the performance of the procedure, and the care of the patient under treatment must follow strict rules, and the requirements should parallel those for major surgical procedures. It is unfair to expect good results from improvised plans or haphazard performances.

C. REQUIREMENTS FOR A GOOD RADIUM IMPLANTATION

1. *Adequate supply of radium needles.* The needles should be adequate in number, length, and in their linear intensity of radium (or other gamma-ray emitters) (Table I). The proper supply of sources is a necessity if implantations with the required geometric pattern and which will deliver the dose in the proper time are to be carried out; we follow Regaud, Paterson,[6] and Martin[4] in prefering the treatment to be protracted between five to seven days. This protraction will give the best results with minimum damage to normal tissues.

2. *Proper indications.* In our Service, interstitial gamma-ray therapy is the treatment of choice of any malignant tumor which requires a localized high dose of radiation, providing it is still limited to an area which can be adequately covered by an implant, and the patient is a good risk for general anesthesia and is able to cooperate during the time that the needles are in place.

3. *A previously determined plan for the geometric arrangement of the sources.* A sketch of the lesion with the possible arrangement of sources is made the day previous to operation. This is used as a guide for the sources needed and as a model in the operating room. When a plan of definite geometric arrangement of sources is followed at operation, the dose delivered by the implant is always calculable.

4. *Careful operative technique.* If it is recalled that interstitial treatment is a precise treatment, it will be realized that general anesthesia is indispensable for the proper performance of the procedure. Proper asepsis, careful measurement and mapping of the patient, good anchorage of each needle by suturing, and good postoperative care are all important factors for successful treatment.

5. *Proper dosimetry.* Accurate calculation of the dose delivered in each case is essen-

Table I

PROPER STOCK OF RADIUM NEEDLES FOR ADEQUATE RADIUM IMPLANTATION (FOLLOWING PATERSON-PARKER)

For Small Center

No. of Units	mg. of Radium	Active Length (cm.)	Actual Length (cm.)	Pt Filter (mm.)	mg./cm.	Total Amount (mg.)
10	.66	1	2 or less	0.5	.66	6.66
10	.33	1	2 or less	0.5	.33	3.33
15	1.33	2	3 or less	0.5	.66	20.0
15	.66	2	3 or less	0.5	.33	10.0
30	1.0	3	4.2 or less	0.5	.33	30.0
30	2.0	3	4.2 or less	0.5	.66	60.0
20	3.0	4.5	5.8 or less	0.5	.66	60.0
20	1.5	4.5	5.8 or less	0.5	.33	30.0
					Total	220

Needles very useful but not indispensable

No. of Units	mg. of Radium	Active Length (cm.)	Actual Length (cm.)	Pt Filter (mm.)
20	1.65	3 (Dumbbell)*	4.2 or less	0.5
15	1.15	3 (Indian club)†	4.2 or less	0.5
20	2.15	4.5 (Dumbbell)*	5.8 or less	0.5

* "Dumbbell" type of needles are "half-intensity" needles (.33 mg./cm.) with extra loading at each end. This extra charge when a row of needles is implanted makes a self crossing.

† "Indian club" type of needles are "half-intensity" needles with extra loading in one end only.

For Large Center

The distribution of the radium should be the same. The number of needles should be greater, especially of 2, 3, and 4.5 cm. active.

tial, in order to obtain consistently the best possible results with a minimum of complications and recurrences and to be able to transmit to others the benefit of one's experience. The means of calculation should be practical and realistic.

D. DOSE-TIME RELATIONSHIP

The scheme of dosage used in our Service is as follows: In general, as a base line we follow Paterson-Parker's dosage system—7,000 r delivered in seven days for rather early tumors in a good tumor bed with good blood supply. This dose-time relationship is modified as follows:

1. The basic dose is decreased (6,000 to 6,500 r in six to seven days) in case of: (a) areas of poor tolerance (axilla, groin, anus, etc.); (b) proximity to sensitive structures (lens of the eye, etc.); (c) very old patients; and (d) large volumes of irradiation, especially involving large portions of bone, normal mucosa, or skin.

2. The basic dose is increased (7,500 to 9,000 r in seven days) in case of: (a) large masses of tumor such as in late tumors of the tongue, floor of the mouth, large and fixed lymph node metastases in the neck; and (b) more resistant types of tumors, such as adenocarcinoma of the salivary glands, etc.

E. INDICATIONS

The main indications for interstitial therapy at the Division of Radiotherapy of the University of Maryland Hospital are as follows:

1. *Head and neck tumors.* In lesions of the *oral cavity*, radium alone is used in (a) most squamous cell carcinomas of early and medium extension; and (b) occasionally in some extensive lip lesions without bone

involvement. It is used in combination with external beam therapy in all large squamous cell carcinomas.

In lesions of the *oropharynx*, radium is used in combination with external beam therapy in some cases.

In lesions of *unusual anatomic locations*, *i.e.*, through bone and cartilage (ethmoid, anterior portion of nasal septum) radium is occasionally used after exenteration of the maxillary antrum or orbit.

For *neck* lesions, radium is used alone in cases of postoperative skin recurrences and in combination with external beam therapy for all medium and large lymph node metastases.

2. *Skin tumors.* Interstitial therapy for skin lesions is used in special cases only.

3. *Breast tumors.* Interstitial therapy is used for recurrences in the chest wall and as a complement to external irradiation in advanced tumors.

4. *Tumors of female genitalia.* Interstitial therapy is used in cases of tumors of the vulva and in groin metastases. It is always used as a complement to external irradiation in tumors of the vagina and in some cases of cervical stump tumors.

5. *Tumors of the anus.* Interstitial therapy is used for early or medium sized lesions of the perianal skin and in some early tumors of the anal canal.

6. *Bladder tumors.* Interstitial therapy is used mostly as a complement to external irradiation in infiltrating, large, well-differentiated tumors.

7. *Tumors of unusual sites.* Interstitial therapy is used in areas not usually implanted: recurrent rectal carcinoma in perineum, vagina and recurrences in the groin, and also in surgically exposed areas: vagina, parametrium, pharynx.

PART II. TREATMENT OF ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK BY INTERSTITIAL RADIUM IMPLANTATION

COMPLEX PATTERNS

Squamous cell carcinoma arising in the mucosa of the oral cavity and upper respiratory and gastrointestinal tract is highly curable by irradiation when the proper treatment is applied early. The treatment of early cases is fairly well established and will not be mentioned here. The discussion will be limited to the treatment of the more advanced stages of the disease.

These tumors exhibit characteristic and fairly constant patterns. Patients who come for treatment present different stages of evolution and extension of the disease, and can be grouped as follows:

1. *Advanced local extensions.* The primary tumor has progressed locally without lymph node metastases in the neck or with only small lymph node metastases in the first echelon of lymphatics (close to the primary). The lesion may invade bone, destroy adjacent organs, impair vital functions, and produce pain, infection and hemorrhage. This comprises a fairly large group of cases (Fig. 1 through Fig. 6).

2. *Advanced metastases in the neck.* In these patients the local extension of the tumor is not the striking feature of the disease; the metastases in the neck lymph nodes are the outstanding signs. In some cases the lymph node metastasis is single but locally advanced to large size, fixed to the vessels and/or bone (Fig. 7); in others the metastases are multiple and even bilateral. These tumors produce little discomfort to the patient. The primary tumor is sometimes early and even difficult to find, but it is more often fairly advanced.

3. *Advanced local disease and metatastases in neck lymph nodes.* Fortunately, this comprises a rather small group of patients. The disease is very advanced in both the primary site and in the lymph nodes (Fig. 8 and Fig. 9).

4. *Postoperative recurrences.* In some institutions this group of patients may be very large. Often the primary lesion has been controlled surgically and the recurrence is in the neck, with or without a radical neck dissection having been performed (Fig. 10). In other instances, the recurrence is in the area of the primary tumor. In many patients the actual disease does not

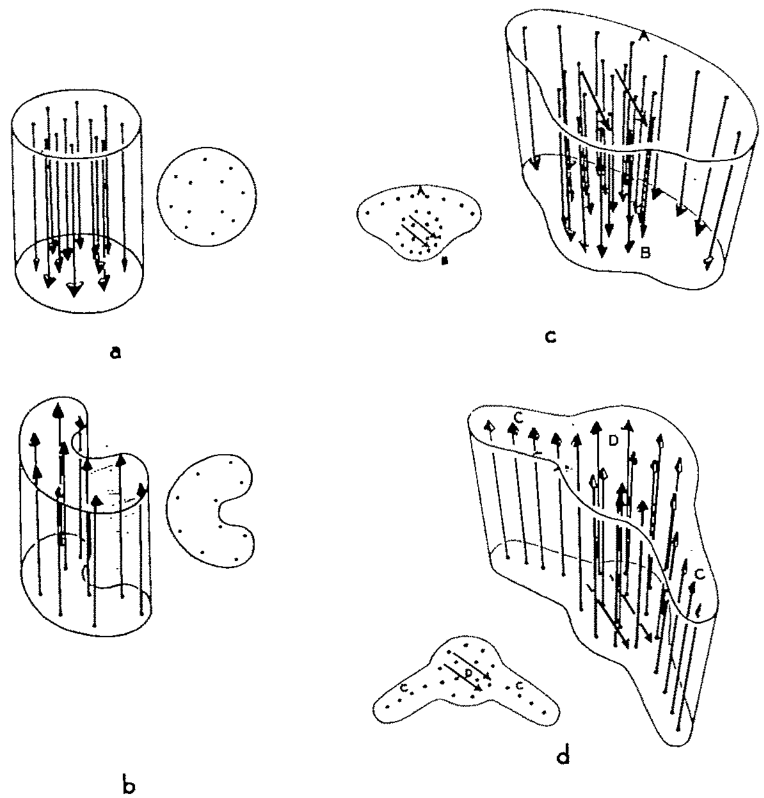

Fig. 1. *Extensive infiltrating carcinoma of the floor of the mouth.* This type of carcinoma carries a very poor prognosis especially when treated by external irradiation alone. A fair number of cases can be better controlled by interstitial therapy, provided the proper implant, often extensive, is used. Depending upon the extent of the disease and the direction of its spread, we have been employing the implants shown in schematic form:

(*a*) In cases of small and medium sized tumors without much infiltration or extension outside the local area, we use a single volume implant for anteriorly placed lesions and a double plane implant for those situated laterally (Fig. 2 and 3). The needles are implanted through the tongue. No crossing is used since this will only increase the reaction in the dorsum of the tongue without contributing to the treatment of the lesion. Silver clips are used to make certain that the position of the needles is correct (Fig. 3).

(*b*) If the tumor shows a definite infiltrating tendency, we add to the intraoral implant a submental one which generally is a curved double plane implant (Fig. 4) or another volume implant, depending upon the shape and size of the submental region. It has been our experience that these tumors have a marked tendency to recur in the submental area if treated by intraoral radium alone. This modification of technique is intended to treat the possible undetected extensions in that direction and has, so far, been efficient in all cases.

(*c*) If the lower gum is invaded by the tumor (including extension into the bone) a palisade-like, curved plane of 2 cm. active length needles (A) is added to the volume (B). This plane is implanted in the buccal and labial mucosa opposite to the extension of the tumor with appropriate margin (Fig. 13).

(*d*) In some patients with lymph node metastases in the submaxillary area or upper carotid chain, the implantation has to be extended to those areas, lateral wings (C) in the submaxillary areas being added to the submental volume (D). Figure 5 shows a case in which an implant of this type was used.

represent a true recurrence but rather residual disease or surgical seeding which reproduces the gross tumor shortly after operation.

5. *Distant metastases.*

The therapeutic management of all these patients is difficult, interesting, and, in many cases, rewarding. In most of the patients, the disease will remain localized above the clavicle for long periods of time and death is usually caused by local extension (infection, pain, functional impairment, and hemorrhage). In disease of this type which is still localized to a rather small

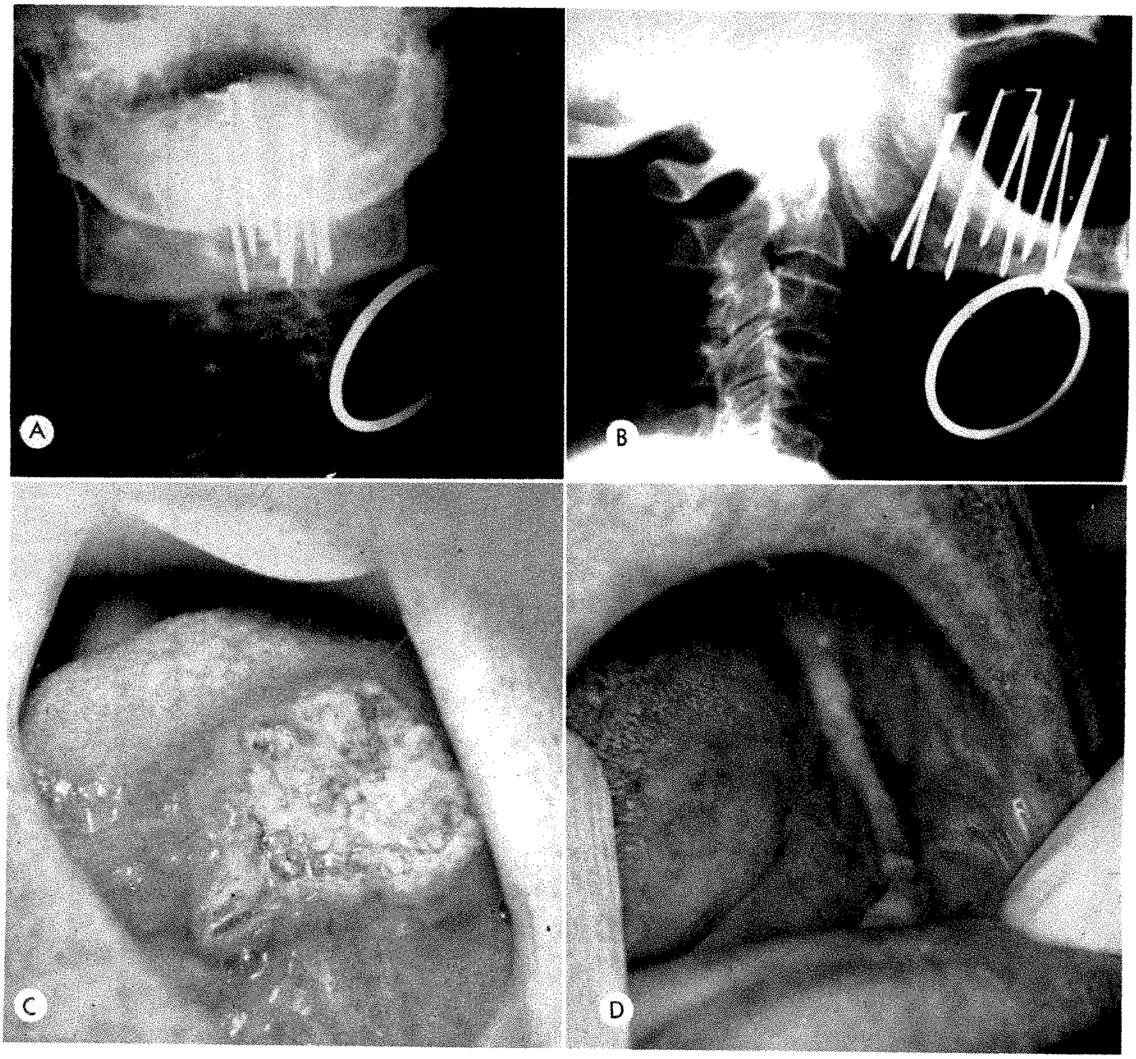

Fig. 2. W.S. 72 W M. *Squamous cell carcinoma of the floor of the mouth, extending to the undersurface of the tongue.*

(*A* and *B*) Double plane implant (dumbbell needles). The clips indicate the medial plane. The patient pulled out the whole implant after 3,500 r had been delivered in 88 hours. Treatment was completed by delivering a tumor dose of 4,000 r in 4 weeks by telecobalt therapy.

(*C*) Lesion before treatment and (*D*) more than 2 years after treatment.

segment of the body there should be little, if any, place for palliative treatment.

All the groups mentioned above deserve radical therapy aiming for a cure even if we know that the chances are that only palliation will be achieved in many cases. With radical treatment the palliation obtained is longer lasting, and some cases deemed hopeless may be brought under control. In fact, nothing less than radical treatment will control extensive, painful, ulcerated primary lesions and alleviate pain and hemorrhage. The local palliation generally achieved justifies radical therapy, even in patients with distant metastases providing the general condition warrants it.

GENERAL CONSIDERATIONS OF TREATMENT

Most of the patients with advanced squamous cell carcinoma of the head and neck present a difficult problem of technique if they are to be treated properly. It

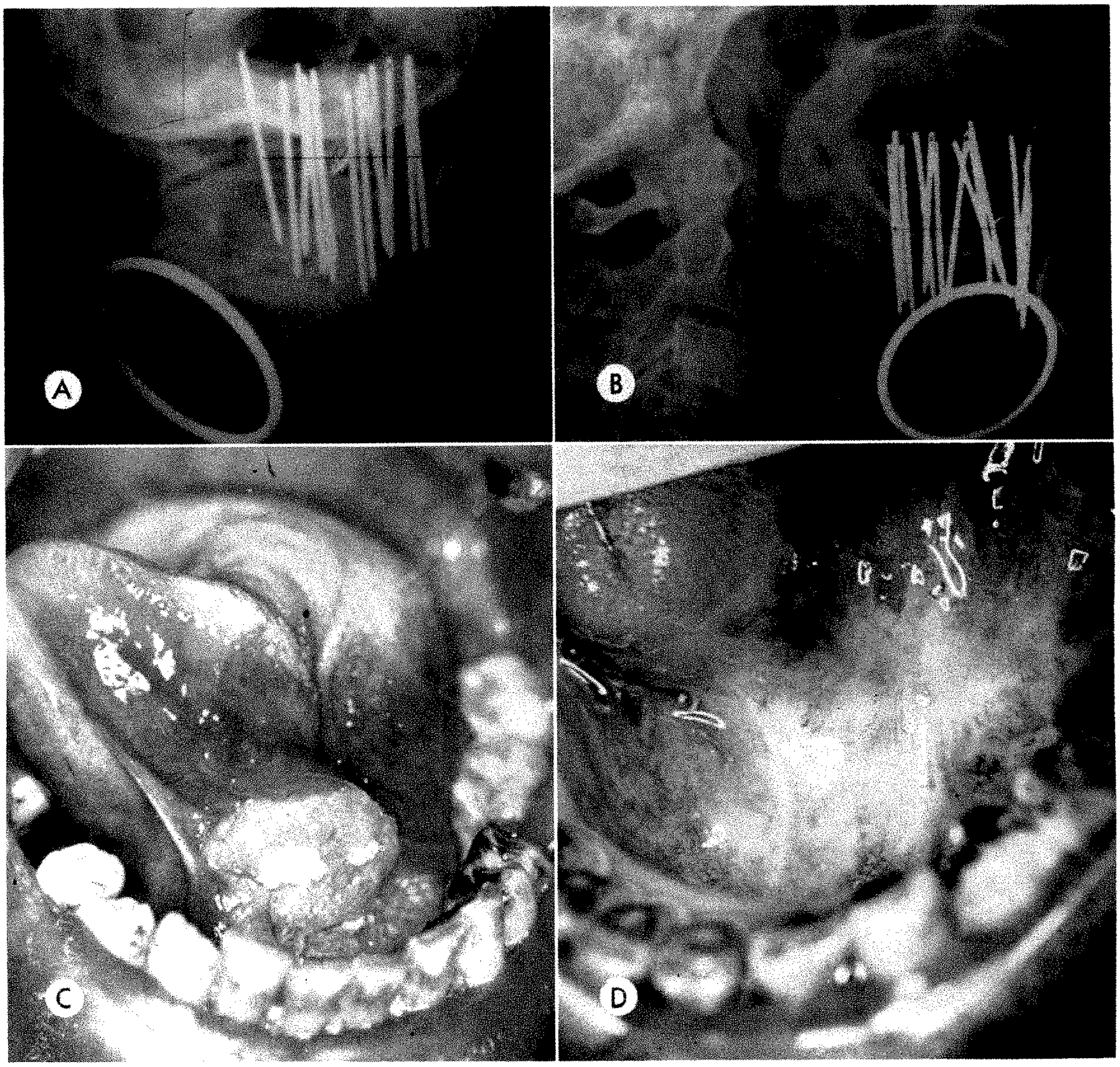

Fig. 3. L.L., 55 W M. *Squamous cell carcinoma of the floor of the mouth, mainly exophytic.*

(*A* and *B*) Single volume implantation without crossing using all half-intensity needles was performed through the tongue. Unless the tongue is fixed by the tumor invasion, it is anchored to the floor of the mouth by a mattress suture, avoiding the lesion. The silver clip marks the level of the lesion. If the roentgenograms show that the clip is not near the middle of the needle length, the implant is unsatisfactory and should be removed. The treatment is then completed by external irradiation. A dose of 7,000 r was given in 6 days.

(*C*) Lesion before treatment and (*D*) 2 years after treatment.

is well known that the majority of squamous cell carcinomas of the head and neck are tumors of moderate radiosensitivity. The dose required for their sterilization is high. In many cases the lethal dose is very close to the maximum tolerance of the normal tissues making up the tumor bed. If external beam irradiation is to be used, especially in cases with neck metastasis, the tolerance is limited by: (1) the large volume to be irradiated, including a great surface of skin, mucosa, bone, and cartilage; (2) the inevitable irradiation of vital structures of limited tolerance, such as larynx, spinal cord, lens of the eye, etc.; (3) the patient's reaction to therapy. The functional impairment due to epithelitis and mucositis produces pain, dysphagia, suppression of salivary flow, etc. In extreme cases, discomfort or starvation may necessitate cessation

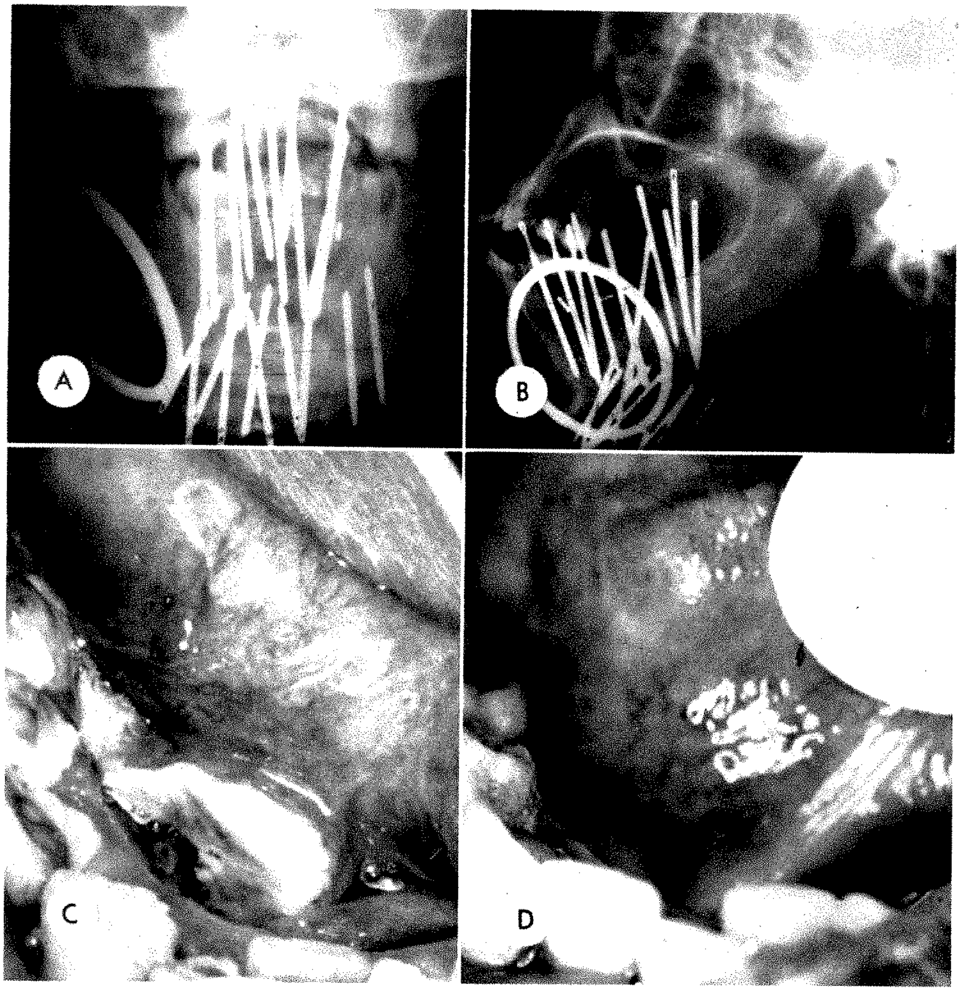

Fig. 4. B.A. 46 N F. *Squamous cell carcinoma of the floor of the mouth, with marked infiltration toward the root of the tongue and the submental region.* The lesion invaded the periosteum but there was no evidence of bone destruction.

(*A* and *B*) Due to attachment to the bone a combined approach was elected. A tumor dose of 3,000 r in 2 weeks was delivered by telecobalt therapy and then radium implantation was performed. It consisted of an intraoral volume and a submental horse-shoe double plane implant as shown in Figure 1*b*. A dose of 3,500 r in 60 hours was delivered by the implants.

• (*C*) Lesion before treatment. (*D*) The lesion in the mouth remained controlled, but the patient died after 2 years with uncontrolled supraclavicular metastases.

of all forms of radiation therapy.

Except for the better tolerance by the skin and bone, the foregoing limitations are no less valid when supervoltage therapy is employed.

In order to reduce the total volume of irradiation and to avoid the inclusion of sensitive structures, interstitial radium may be used. In many of these cases a radium implantation can be devised which will properly irradiate the primary lesion and the metastases in the neck, if present, delivering a very small dose to the larynx, pharynx, or spinal cord. In cases where it is doubtful that the radium implant is satisfactory at the beginning of therapy, another alternative may be considered: a combination of external irradiation (conventional or supervoltage) and radium implantation.

Interstitial radium therapy has an important area of application in the treatment of postoperative recurrences of head and neck tumors, most of which arise in a poor

tumor bed with a disturbed blood supply surrounded by considerable scar-like fibrous tissue. Because of this, they are more resistant to irradiation. They require a higher dose and the technique of treatment is generally more difficult, particularly since the tissues have a poor tolerance to irradiation. Interstitial radium therapy is preferable in most of these cases since the dose can be raised to higher levels without danger of producing permanent damage in the normal tissues.

In the treatment of advanced tumors of the head and neck with any technique, radium alone or combined with external beam therapy, it is always advisable to deliver a higher dose where the mass of the tumor is larger and a lower dose to the less voluminous peripheral extensions of the tumor. This is in agreement with two general principles of irradiation of cancer, originated at the Fondation Curie (Paris) and stressed by Fletcher in this country. They are: (1) the central portion (the older part) of the tumor is more resistant to irradiation than the periphery (the growing, younger part) and (2) the sensitivity of any tumor is in inverse ratio to its size.

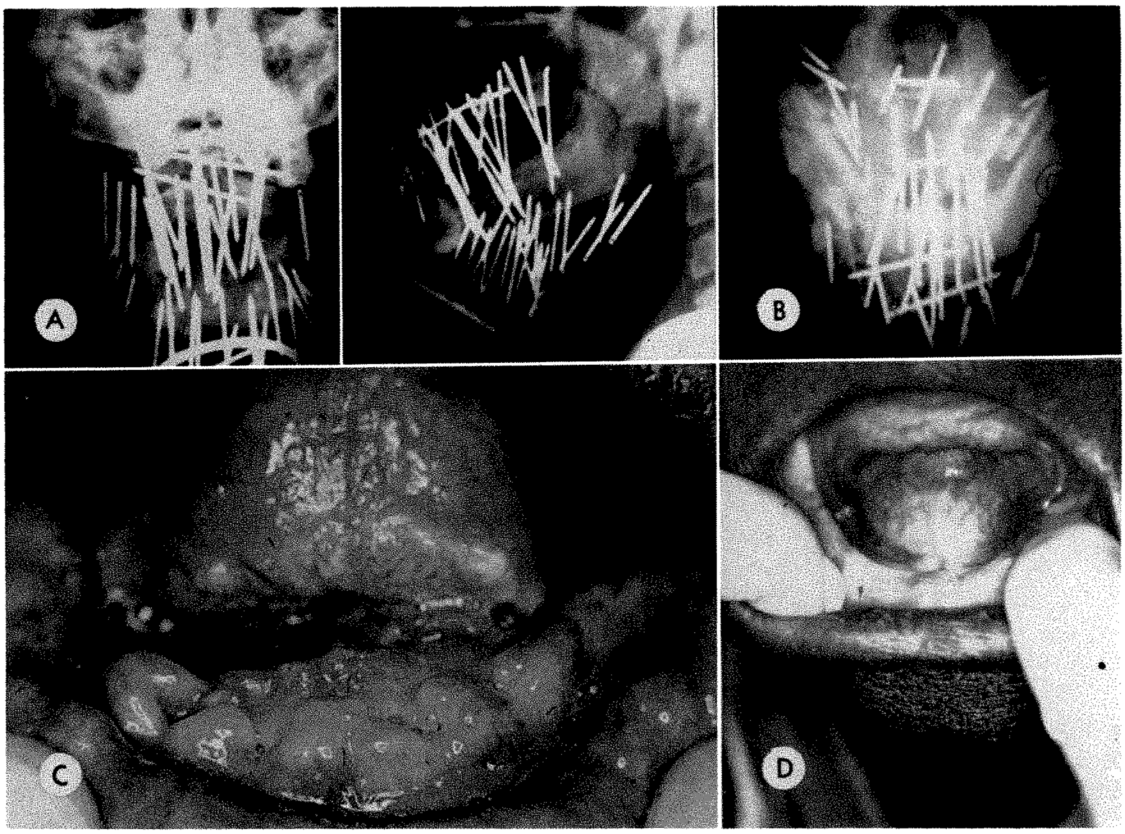

Fig. 5. L. B. 59 N M. *Extensive infiltrating squamous cell carcinoma of the floor of the mouth.* There was involvement of the root and anterior two-thirds of the tongue which was almost completely replaced by tumor; the lower gum was extensively involved and there was questionable bone invasion. Several small hard lymph nodes were palpable in both the submaxillary and the submental regions.

(*A* and *B*) Radium implants of a complex pattern were used, composed of 2 volume plus a palisade curved plane implant for the primary lesion and a single plane implant of full-intensity needles for both submaxillary areas. Both carotid chain areas of the neck were treated "prophylactically" by telecobalt therapy. The dose was 6,500 r in 103 hours for the primary lesion and its extensions; 6,000 r in 99 hours for the submental implant; and 7,000 r in 60 hours at 0.5 cm. for each submaxillary plane.

(*C*) Lesion before treatment. The irradiation and its reaction were very well tolerated by the patient. He had a residual ulceration in the area of the frenulum which took almost a year to heal. (*D*) The patient is free of disease after 2 years. The radiation changes in the tissues are minimal.

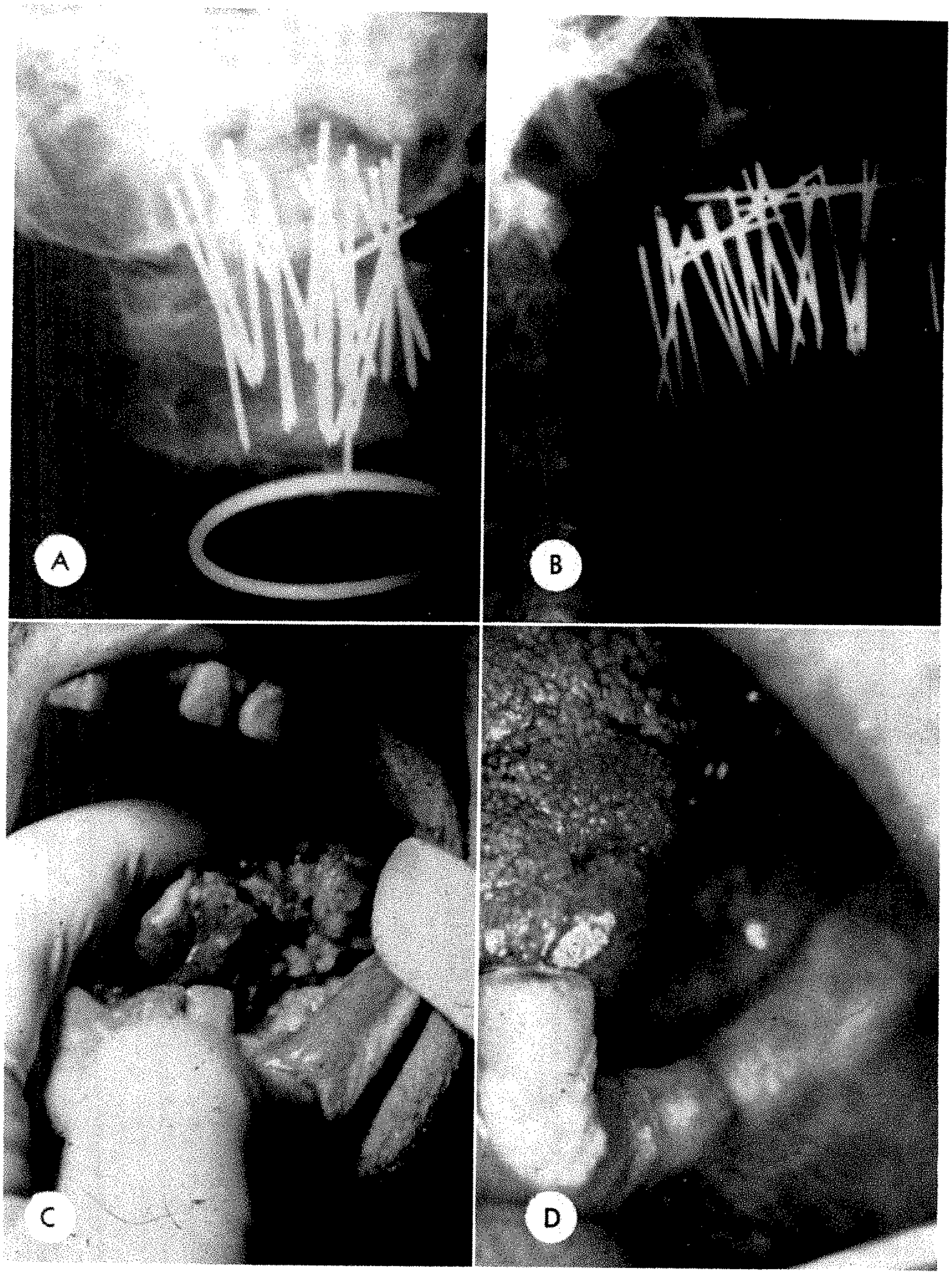

Fig. 6. C.H.P. 57 W M. *Extensive squamous cell carcinoma involving the whole of the tongue (anterior two-thirds and base) and the entire left side of the floor of the mouth.* The patient had several bilateral hard neck lymph nodes and was in a very poor general condition. It was decided to treat the primary lesion by interstitial radium implantation and the neck by telecobalt therapy.

(*A* and *B*) An extensive volume implant was used including the whole tongue and the left floor of the mouth. The implant was satisfactory but due to the extensive necrosis present in the tumor, some of the needles were frequently dislodged. It was, therefore, decided to remove the implant after 4,200 r had been delivered in 66 hours and to complete the treatment with telecobalt therapy, 3,000 r in $2\frac{1}{2}$ weeks. Both sides of the neck received 5,500 r tumor dose in 4 weeks.

(*C*) Lesion before treatment. (*D*) The primary tumor regressed, but there was always a small indurated ulceration on the left side of the tongue with residual tumor which enlarged terminally. The patient died in 6 months with uncontrolled neck metastases (in the irradiated area). The failure to control both the primary lesion and lymph node metastases could be due to the very poor general condition of the patient and the advanced stage of the disease. A higher dose would not have achieved a better result in this case.

It is not uncommon in head and neck tumors to have recurrences, regional metastases and even development of consecutive primary lesions after the original therapy has been completed. As long as the lesion appears to be localized to the head and neck, the patient should not be abandoned, particularly if the primary lesion has been under control for several months or years. The ability to treat near or even within a previously irradiated area by the use of an implant may allow a life to be prolonged with comfort, occasionally for a matter of years.

TECHNIQUE

For the treatment of early lesions the Paterson-Parker system of radium distribution and calculation is the one which best serves the clinical requirements. However, the Paterson-Parker system provides only for the use of a single geometric pattern of radium arrangement, *i.e.*, single plane, double plane and volume implants. It does not provide for complex combinations of single patterns. The other system still in use is the empirical procedure of placing the radium needles in parallel pattern, 1 cm. apart, in a plane or volume, having all the needles of the same intensity. The dose delivered by the latter system is difficult to calculate with clinical accuracy in extensive implants. Without adequate dosimetry it is impossible to predict either the reaction of the normal tissue or the sterilization of the tumor. The extensive radium implantation necessary for the treatment of advanced lesions of the head and neck can be performed with success providing a definite

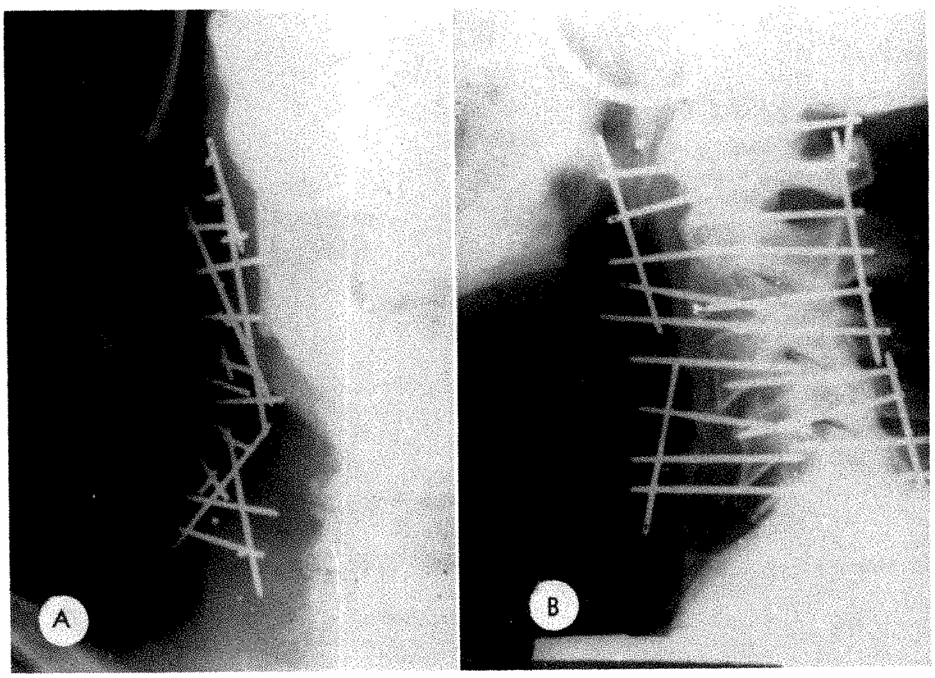

Fig. 7. I.B. 65 W M. *Carcinoma, cylindromatous pattern, involving the right side of the neck in the upper carotid region from the tail of the parotid gland.* The patient came for therapy after a local excision of the tumor mass was performed. It was decided to use combined 220 kv. roentgen therapy and radium implantation, starting with single field external beam therapy.

(*A* and *B*) The implant covered the same area as the field of external irradiation and consisted of a fully crossed single plane application. The patient was lean with a very thin layer of tissue between the carotid and the skin, and a single plane was considered adequate. The dosage was as follows: external beam therapy: upper neck—4,000 r tumor dose in 4 weeks; lower neck—3,000 r tumor dose in 4 weeks; radium implant: 4,000 r at 0.5 cm. from the plane in 73 hours. The reaction was mild.

The patient expired due to intercurrent disease 16 months after therapy without evidence of active disease in the neck. The radiation changes were minimal.

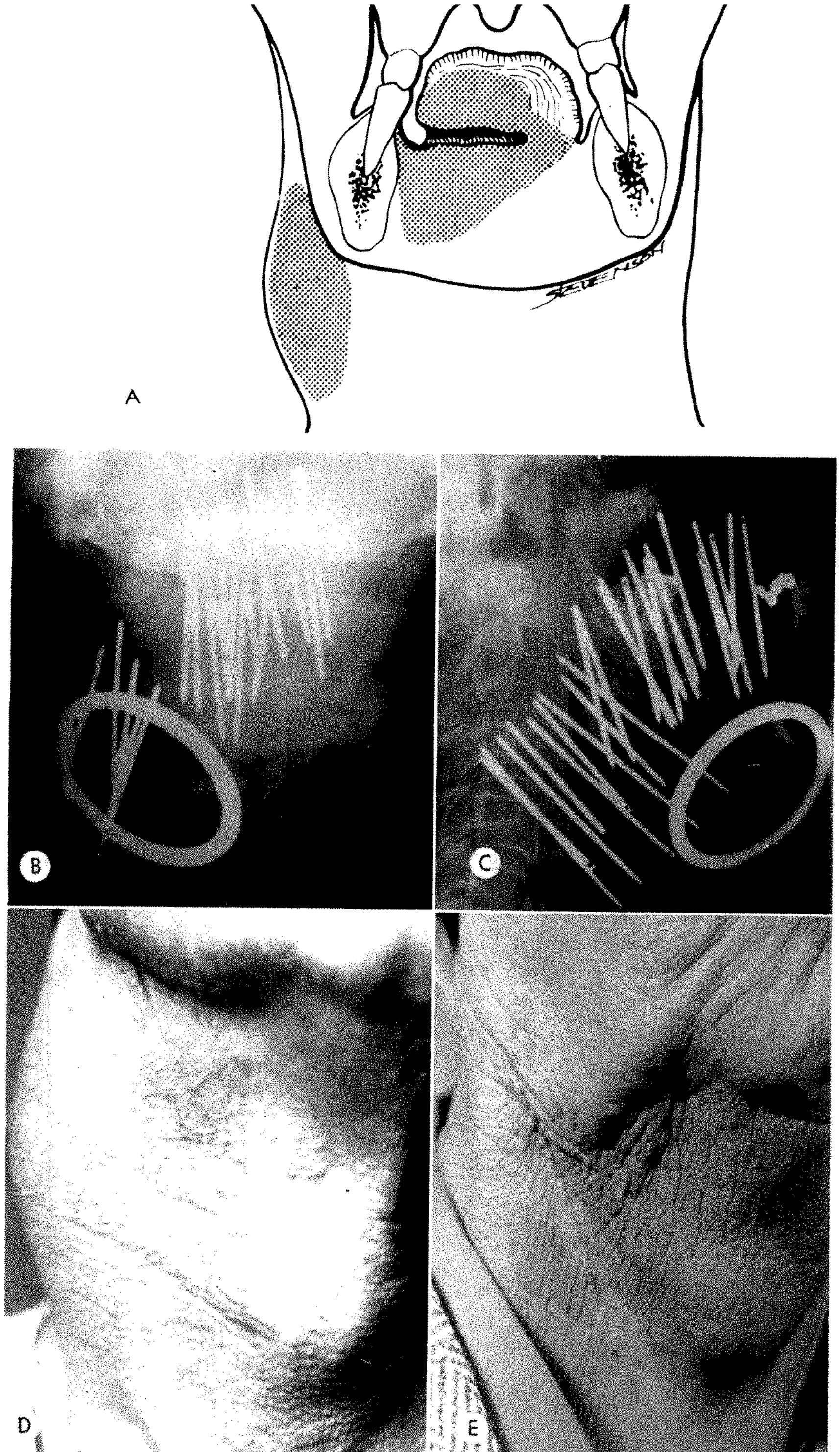

FIG. 8. R.B. 60 W M. *Squamous cell carcinoma, deeply infiltrating, of the right undersurface of the tongue with bilateral extension into the root of the tongue and floor of the mouth.* A deep ulceration almost severed the tongue from its roots (a poor prognostic sign in our experience). Three lymph nodes on the right side of the neck were palpable; the largest 5 cm. in diameter, was proved positive by biopsy.

(*A*) Sketch of extent of the lesion. It was decided to use combined telecobalt therapy and radium implantation. The treatment was started with telecobalt therapy to both the primary tumor and the right side of the neck. After the third week the patient developed repeated copious hemorrhages from the ulceration (lingual artery involvement?) which required ligation of the external carotid artery. This delayed the treatment for one week.

(*B* and *C*) The radium application consisted of a volume implant including the tongue and both sides of the floor of the mouth, and a double plane implant, of half-intensity needles, without crossing, for the residual disease in the right neck. The dosage was as follows: telecobalt therapy: 5,000 r tumor dose in 6 weeks to both the primary lesion and the neck; radium implant: 2,000 r in 35 hours for the primary lesion and 2,500 r minimum in 35 hours for the lymph nodes.

(*D*) Swelling of the neck, due to metastatic lymph nodes before treatment. (*E*) The metastatic lymph nodes of the neck disappeared after treatment, leaving some indurated edema. The primary lesion also regressed, but a flat ulceration remained on the right floor of the mouth from which a positive biopsy was obtained months after therapy.

system is followed in the radium distribution and in the arrangement of sources in geometric patterns. If the needles with proper loading of radium are placed in a definite geometric pattern, the dose delivered in each case is calculable with clinically useful accuracy.

The majority of radium implantations necessary for the treatment of the lesions under discussion call for the combination of

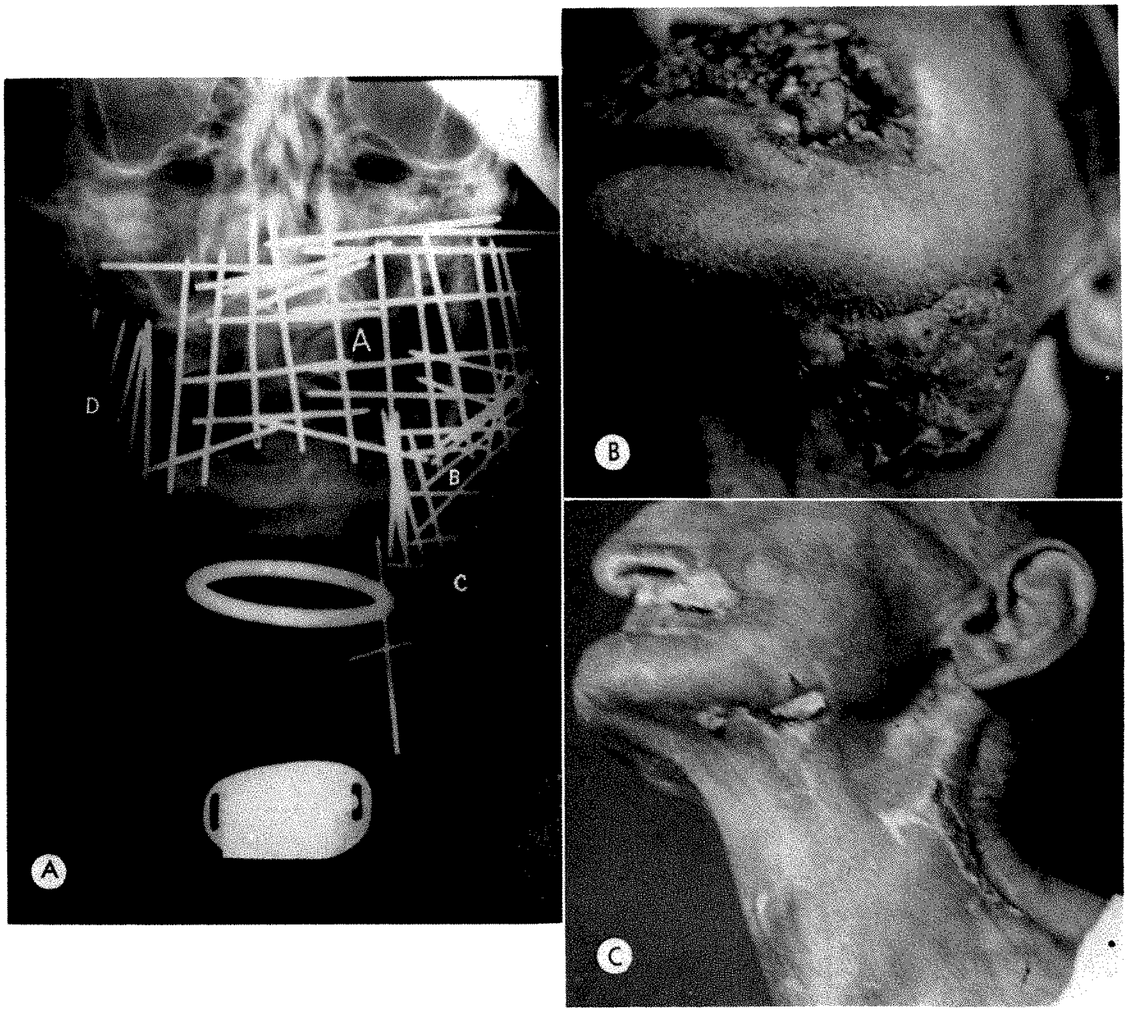

Fig. 9. J.W.S. 66 N M. *Squamous cell carcinoma of the left commissure of the lip with marked extension into the buccal mucosa, whole upper lip and portions of the lower lip and left cheek.* Large ulcerated lymph node metastases (6 cm. in diameter) were present in the left submaxillary region, and two other hard lymph nodes (2 cm. in diameter) were palpable in the upper carotid area. The right buccal mucosa was replaced by a verrucous type of leukoplakia and carcinoma *in situ.* The patient was in a very poor general condition. Only interstitial radium was used.

(*A*) A complex pattern implantation was performed by three consecutive teams of operators. The main features of the pattern were: 2 planes for the primary lesion (A), 3 planes in a triangular arrangement for the submaxillary lymph nodes (B), a single plane of dumbbell needles for the right buccal mucosa (D), and a single plane for the lymph nodes in the left upper carotid area (C). The doses delivered were: 6,000 r in 86 hours for the primary lesion; 8,000 r in 80 hours for the submaxillary lymph nodes; 9,000 r at 0.5 cm. in 92 hours for the upper neck plane; and 6,000 r at 0.5 cm. in 157 hours for the plane in the right buccal mucosa.

(*B*) Extent of lesion before treatment. (*C*) The patient tolerated the treatment very well and the improvement was immediate.

Comment. When the bulk of the tumor is large and most of the implant is held within it, the tolerated dose can be very high. Bulky tumors of the squamous cell type, especially in neck metastases, require very high doses of irradiation if control is to be achieved.

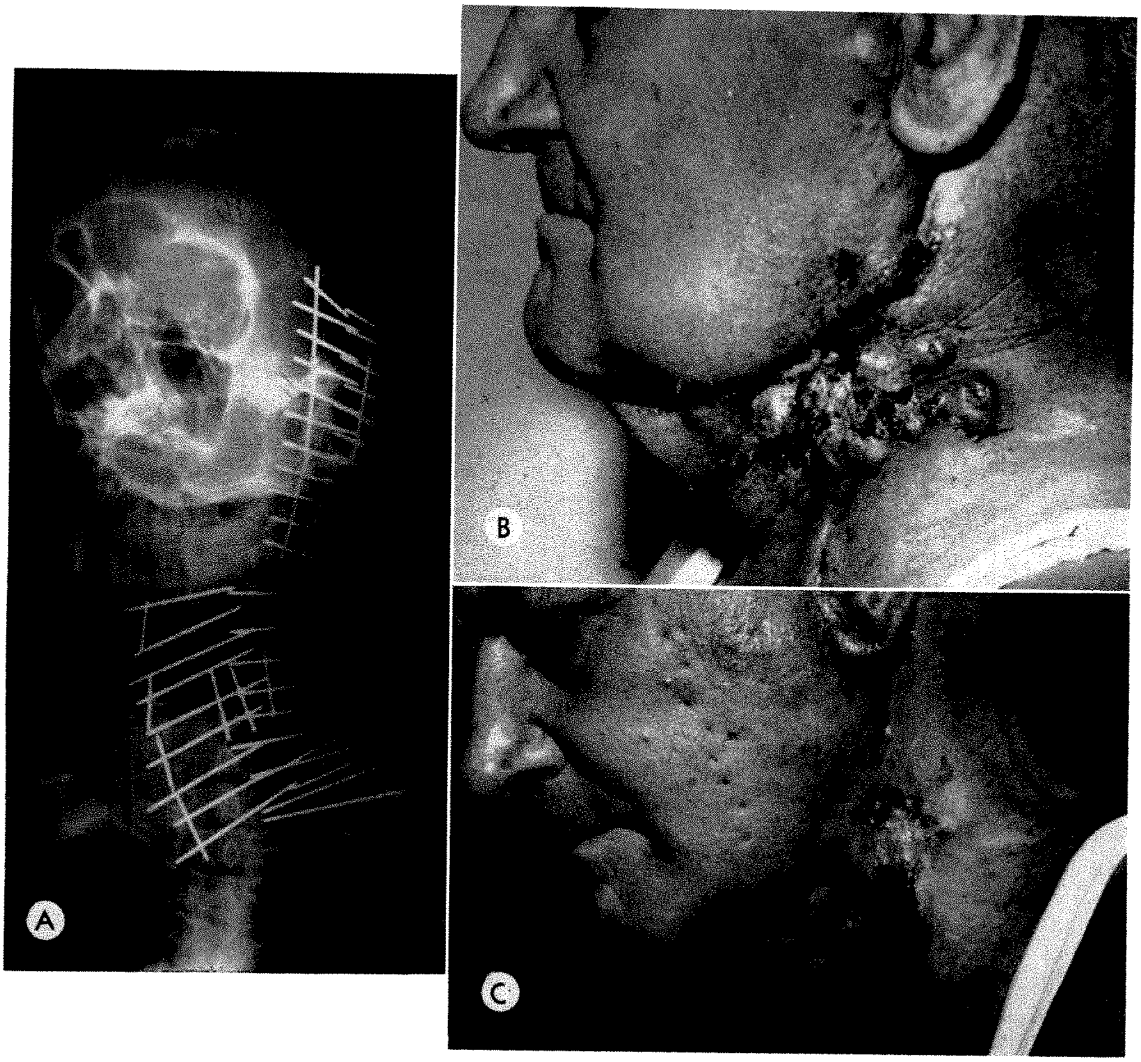

Fig. 10. C.B. 58 W M. *Squamous cell carcinoma of the left side of the neck with left preauricular lymph node metastases, recurrent after radical neck dissection.* The primary lesion in the buccal mucosa, previously treated by irradiation (conventional roentgen rays and interstitial radium), was under control. The disease infiltrated the whole left side of the neck from mastoid to clavicle. Only interstitial radium implantation was performed.

(*A*) A complex pattern radium implant was employed covering satisfactorily the whole of the gross detectable disease except for the posterior portion of the supraclavicular area where treatment was complemented by external beam therapy. The implant was of a parotid plus whole neck type, making use geometrically of a combination of single and double planes. A dose of 9,000 r in 190 hours was delivered to the area where the tumor was bulkiest, and 7,000 r in 68 hours to the rest of the implanted area. The supraclavicular region received 4,000 r in 2 weeks with 220 kv.

(*B*) Extent of lesion before treatment. (*C*) Two months later no tumor was detectable clinically, and the patient was back at work. The patient died of distant metastases 10 months later with the treated areas free of disease.

Comment. This patient was treated by interstitial therapy as part of a special study. The local control of the disease was remarkable in this and other similar cases. This type of implantation should not be performed as a routine procedure because of the exposure involved unless the organization of the department permits the performance by several teams of operators or, even better, the use of nylon threaded gamma-ray emitters.

two or more geometric patterns of radium arrangement. It is possible in most of the cases to encompass these lesions by a more or less complex type of implant and, providing the geometric pattern is followed, still have control of the dose delivered.

Homogeneity is not always desirable throughout the radium implant. On the

contrary, following the principle mentioned above, it is better in advanced and bulky lesions to deliver a higher dose to the core of the tumor. It is also more advantageous to have radium needles of such linear intensity as to be able to deliver the total dose in five to seven days, to better spare the normal tissues.

It should be remembered that this type of therapy compares in its extent with radical surgical procedures such as the commando operation, glossectomy (partial or total) plus neck dissection, etc. The surgical procedures are always previously planned; definite steps are followed during their performance as well as during the post-operative period. Radium implantations for any lesion require just as definite a plan if consistent results are to be expected.

Before undertaking this type of therapy, the patient should be put in the best possible physiologic state. Special attention should be paid to the blood volume, hemoglobin and hematocrit, serum protein level, and the fluid and electrolyte balance. The nutrition should be improved, if necessary by way of nasogastric tubes or intravenous fluids and the infections should be treated. In most of the cases the treatment of the neoplasm is not an emergency and by improving the general condition of the patient, the effectiveness of the irradiation is enhanced. In many cases ancillary procedures such as tracheostomy, the extraction of decayed teeth, etc., are necessary.

The care of patients while the implant is in place is also important. No less important is the care thereafter; pain relief, oral hygiene, and proper feeding may mean the difference between success and failure.

In most of the cases in this group, the type of implant required is of the complex pattern variety. Such implants are tailored to the disease and its extensions by using a combination of single patterns: volume and planar. Any single component can be repeated as often as required, providing no undesired hot or cold spots are formed. The usual rules of radium distribution for single patterns must be altered in some complex implants as the case requires, *i.e.*, the end of the plane close to another implant should not be crossed if a hot spot is to be avoided; some implantations are performed either with full or half intensity needles in order to obtain a more suitable isodose.

DOSAGE

The general scheme of dose-time relationship already mentioned is followed. In very extensive implants the dose delivered is highest at the site where the tumor is bulkier and lowest in the areas where the tumor is not clinically demonstrable, but which are potentially involved by microscopic extensions. This variation in the dose delivered is achieved by taking advantage of the different loadings of the needles and by removing parts of the implant at different times. Each component part of an implant is calculated separately and its contribution to the other parts considered. It is very useful to thread needles of different loadings with different colored threads, and it will help in the calculation of the different portions of the implant to have a detailed sketch of the needles made simultaneously with the implantation.

SUMMARY

1. Advanced squamous cell carcinomas of the head and neck, even with neck metastases, are tumors which remain localized above the clavicle for relatively long periods of time.

2. In all cases radical therapy should be the treatment of choice even if in many cases the result will be palliation only. With this policy more cures and better palliation can be obtained.

3. In this group of patients interstitial treatment should be performed whenever possible because of the reduced irradiation of normal tissues and the enhanced probability of cure due to the previously mentioned advantages.

4. Postoperative residual or recurrent tumors are often best treated by interstitial gamma-ray therapy.

5. Careful preoperative care, planning and performance of the implant and postoperative care are of paramount importance in obtaining the best results.

6. Careful follow-up with adequate treatment of new tumor foci as they appear will allow long survival free of symptoms, in many cases of advanced tumors of the head and neck even where a cure is not obtained.

7. Extensive interstitial treatment is possible in the head and neck lesions and encouraging results can be obtained when the proper indications and techniques are followed.

PART III. COMBINED EXTERNAL BEAM IRRADIATION AND INTERSTITIAL THERAPY IN HEAD AND NECK TUMORS

GENERAL CONSIDERATIONS

Based upon the general principles already discussed, efforts were made to reduce the volume of heavy irradiation, particularly the unnecessary irradiation of normal tissues, in the treatment of head and neck tumors whenever possible. This became more important with the increasing use of supervoltage therapy since this modality, in general, does not reduce the volume of normal tissue irradiated. On the contrary, with the increased depth dose characteristic of this type of therapy and the popular use of two parallel-opposing fields, the volume of heavy irradiation, in most cases, extends from side to side of the face and/or neck with inclusion of much normal tissue, as well as the tumor, between the fields. The dose delivered by such a technique is sometimes higher in tissues outside the tumor bearing area than in the tumor itself (Fig. 11).

In search of a better tecnhical arrangement to deliver a lethal dose to a tumor bearing area when only conventional therapy of 1 mm. Cu half value layer was available to us, we began to study the possibilities of the combined technique of external beam irradiation and interstitial therapy. When cobalt 60 teletherapy in combination with interstitial treatment was investigated, it became obvious that such an approach had the same advantage of reducing the volume of high irradiation with the additional benefits intrinsic to supervoltage therapy (Fig. 11). Perhaps, by the use of a short-distance cobalt or cesium unit combined with a radium implant, the maximum benefits of this technique might be obtained—the further reduction of the volume of high irradiation together with the advantages of supervoltage external beam therapy.

The dosimetry of the combined technique is illustrated in Figure 12.

The concept of combining external beam and interstitial therapy is not a novel one in treating head and neck tumors. Indeed, several schools of radiation therapy have been using it for years (McWhirter, Fletcher, Martin, and others) and found it to be of definite value.

PRINCIPAL MODES OF COMBINATION

We have used the following principal modes of this combination:

GROUP 1. *Interstitial gamma therapy as a complement of external beam therapy.* Here, the fundamental part of the treatment is the external beam irradiation. In these cases the dose to the normal tissues is close to the tolerance level, but, at the end of treatment, there still remains a considerable amount of residual tumor at the site of the primary lesion and/or in the neck lymph nodes. This indication is related to the principle mentioned before of delivering higher doses to the bulkier portion of the tumor (see Part II).

This procedure is of greatest value in cases of well-differentiated carcinomas, particularly those of the floor of the mouth, base of the tongue or retromolar trigone, in some tonsillar and peritonsillar tumors, and with large lymph node metastases in the neck. In all cases an effort is made to keep the implant within the residual tumor itself in order to further spare the normal tissues (Fig. 13, 14 and 15).

GROUP 2. *External beam therapy as a complement of interstitial radium therapy.* This

method is used in cases where the important part of the treatment is the radium implantation, and the external irradiation is added as a complement. These cases can be subdivided into two categories:

(a) External irradiation before the interstitial irradiation. This type of therapy is indicated in the cases where interstitial irradiation is the treatment of choice but where complete coverage of the tumor by an implant cannot be assured, either because of its extension or anatomic location. The external irradiation is intended to reduce the extent and the volume of the tumor in order to ensure that the whole tumor bearing volume can be properly covered by the implant. The main indications are large lesions of the floor of the mouth with extension close to, or involving bone; extensive buccal mucosal lesions involving the pterygoid region, the anterior pillar, or lower or upper gum; postoperative recurrences of parotid tumors or neck metastases, and very extensive lesions of the tongue with invasion of the floor of the mouth close to or invading the lower gum (Fig. 16, 17 and 18).

(b) External irradiation after the interstitial radium. This sequence is followed in cases where roentgenograms show that the pattern of the implant is not completely satisfactory, with either questionable cov-

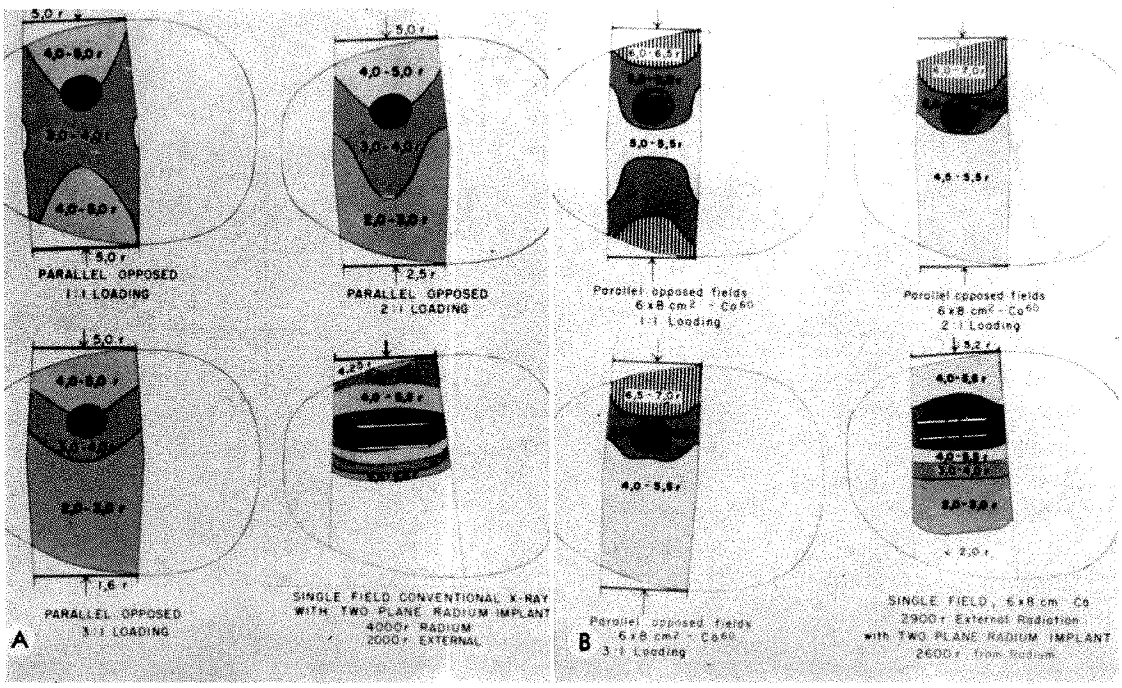

Fig. 11. These figures show the different volumes of heavy irradiation (above 5,000 r) with the varied techniques commonly used for a tonsillar tumor.

(*A*) *Technique with conventional roentgen rays* (220 kv., 1 mm. Cu half value layer). With conventional roentgen therapy and a 2 parallel-opposing field arrangement, it is very difficult to obtain a lethal dose for squamous cell carcinoma unless the tolerance of the normal tissue is exceeded. Differential loading will improve the distribution of dose and will diminish the unnecessary heavy irradiation of normal tissues. Single field external beam combined with interstitial radium is the best arrangement for delivery of the proper dose to the desired site with a minimum of irradiation of the normal tissues.

(*B*) *Technique with telecobalt* (50 cm. distance). The above comments also apply here. The volume of heavy irradiation is larger than for 220 kv. roentgen rays. The advantages of differential loading are not as important as with conventional beam therapy. Again the best arrangement of dose distribution is with external cobalt beam and interstitial radium. The radium implant does not have to be of a double plane pattern. In most of the cases a single plane will build up the dose from within satisfactorily. For most tumors situated laterally, the best technique of treatment would probably be achieved by using short-distance cobalt or cesium external beam therapy and a radium implant.

erage of the whole lesion or lack of uniform dosage (Fig. 19), and where the radium needles have not maintained their position during treatment, or when one or several needles have become dislodged from their proper places, necessitating premature removal of the implant (Fig. 20).

GROUP 3. *External beam therapy and interstitial therapy equally important.* In the techniques already described, implantation procedures are planned and executed with the intent to encompass the entire lesion. In this group of cases such coverage is not necessary. The implantation of radioactive sources is planned and executed so as to provide an internal field of irradiation. The aim is to produce between the external irradiation field and the "interstitial field" a proper volume of high dose irradiation which will adequately cover the tumor bearing tissues. This can usually be achieved by a single plane implant, although sometimes a double plane implant is required. It is not necessary to "cover" the whole tumor in the transverse diameter because the irradiation of the outer portion of the tumor volume is provided mainly by the external beam.

Here, the combination technique is used as an *established technique of choice and both external and interstitial irradiation are equally important* in the management of the lesion. In this group of patients the lesion is treated by an external field of irradiation (external beam roentgen rays or cobalt 60 teletherapy) and the "internal field" created by the radium implant. This technique makes full use of all the advantages of the combined procedure (Fig. 11). It is especially indicated for lesions involving laterally placed structures. The main indications are: some large tumors of the buccal mucosa, lesions of the buccinator region, retromolar trigone, some lesions of the lateral portion of the floor of the mouth, especially with extension into the lower gum, lesions of the gums, lesions of both upper and lower buccal gingival sulci, some lesions of the tonsil and peritonsillar regions (palatoglossal and glossotonsillar sulcus), some large metastases in the neck, and large inoperable lesions of the parotid gland (Fig. 21, 22 and 23).

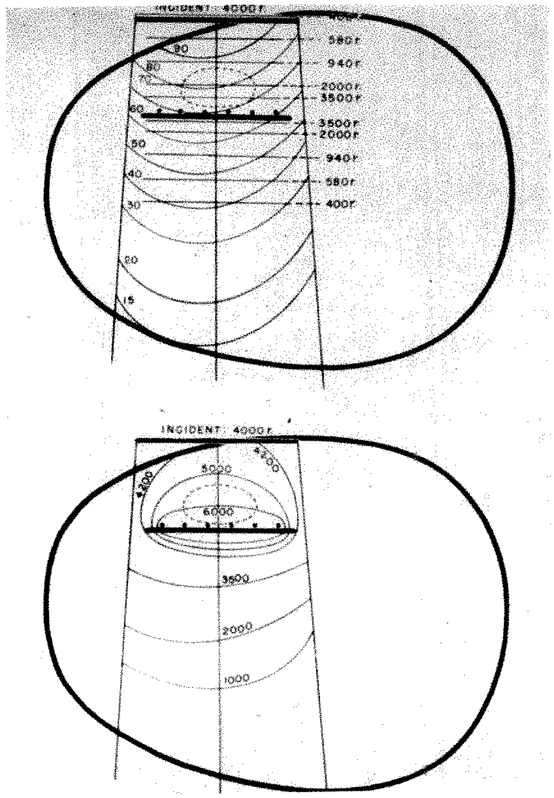

FIG. 12. *Dosimetry.* In all cases where a combined technique is employed, the dose is calculated as indicated in this sketch by observing the following steps: (1) an accurate contour of the patient is drawn at the proper level; (2) the isodose curves of the single field of external irradiation are marked in, allowing for the inverse square law correction; (3) an accurate localization of the lesion and radium implant is made with respect to the contour by direct measurement on the patient and roentgenographic films; (4) the output of the implant every 0.5 cm. is superimposed on the isodose curves from the external beam; (5) at every intersection of two lines, the doses are added and a combined isodose curve is made showing the total contribution from both sources.

We are aware that the addition of the conventional 220 kv. to gamma radiation is not biologically correct; however, this procedure has been useful in establishing a basis of technique and dosimetry.

DOSAGE

Whenever possible the dose delivered by the single field is kept well within tolerance of the normal tissues. In cases where conventional energies are used, we try not to exceed 5,000 r skin dose. When super-

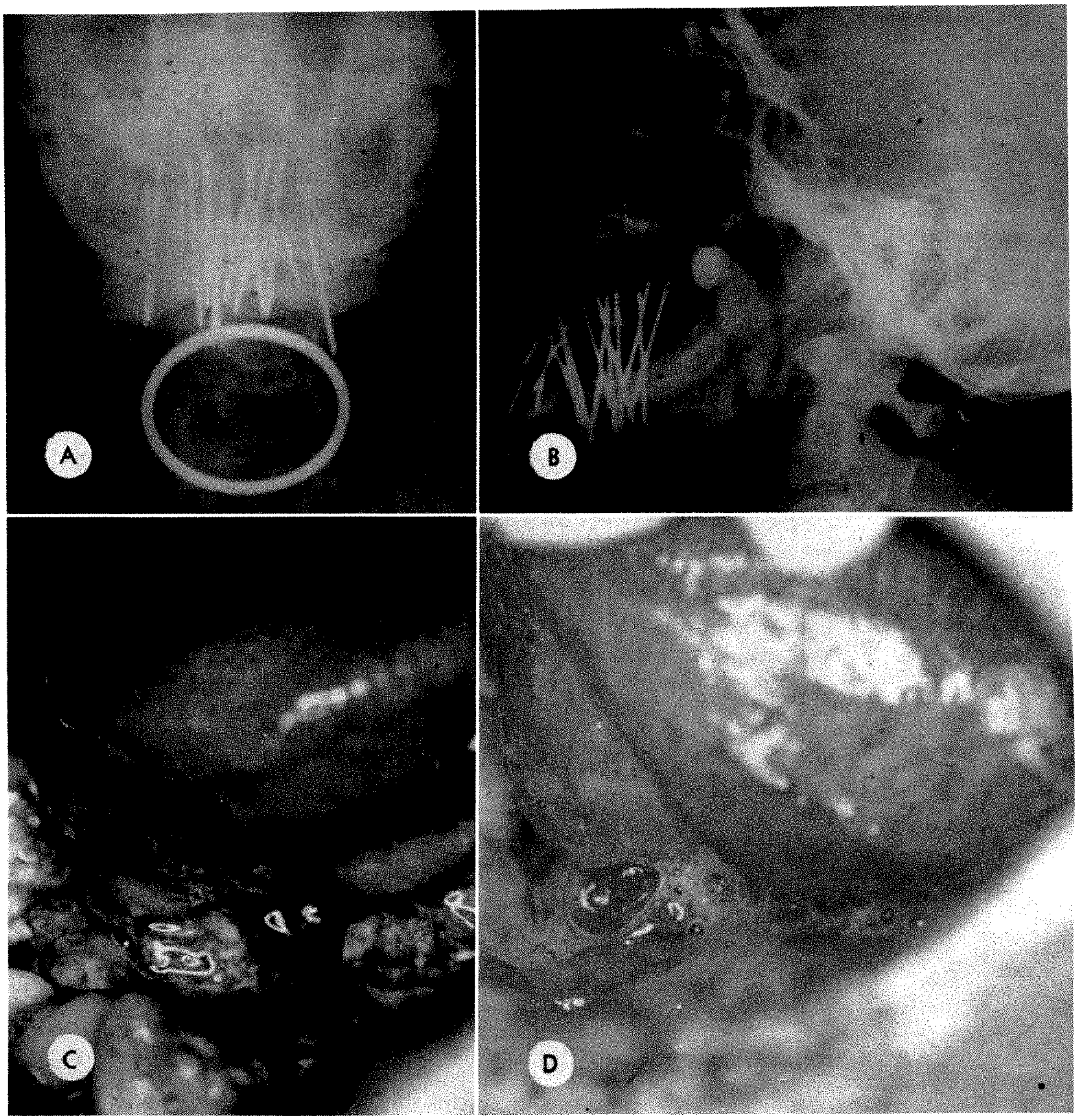

FIG. 13. C.F. 55 W M. *Squamous cell carcinoma of the floor of the mouth, anterior portion, with extension toward both lateral portions.* The gum was involved anteriorly with invasion and exposure of the bone. A submental lymph node, 1.5 cm. in diameter, was palpated. The patient was in a good general condition. Due to the extension of the disease and the amount of bone involvement, it was decided to treat the primary lesion and both lymph node bearing areas with telecobalt after which a radium implant was placed into the residual tumor itself.

(*A* and *B*) The implant consisted of a single volume through the tongue, and extended out to the periosteum anteriorly and laterally. A curved palisade-type of plane was added to cover the area of gum and bone invaded by disease. With telecobalt therapy the primary lesion and upper neck received 5,800 r tumor dose in 5 weeks and both supraclavicular areas and lower neck 5,000 r in 4 weeks. The implant, applied 2 weeks after the external therapy was finished, added 1,000 r in 20 hours.

(*C*) Lesion before treatment. (*D*) The major portion of the lesion regressed one month after therapy. On the floor of the mouth, anteriorly, close to the bone, a small ulceration with an indurated base remained, without symptoms. Ten months later the induration increased and a positive biopsy was obtained from the area. Surgery was performed a year after therapy, and the patient died of septicemia produced by a postoperative infection.

Comment. This patient obtained a year of comfortable life from the treatment. There is no doubt that the heavy irradiation contributed to the poor defense shown by the tissues against infection.

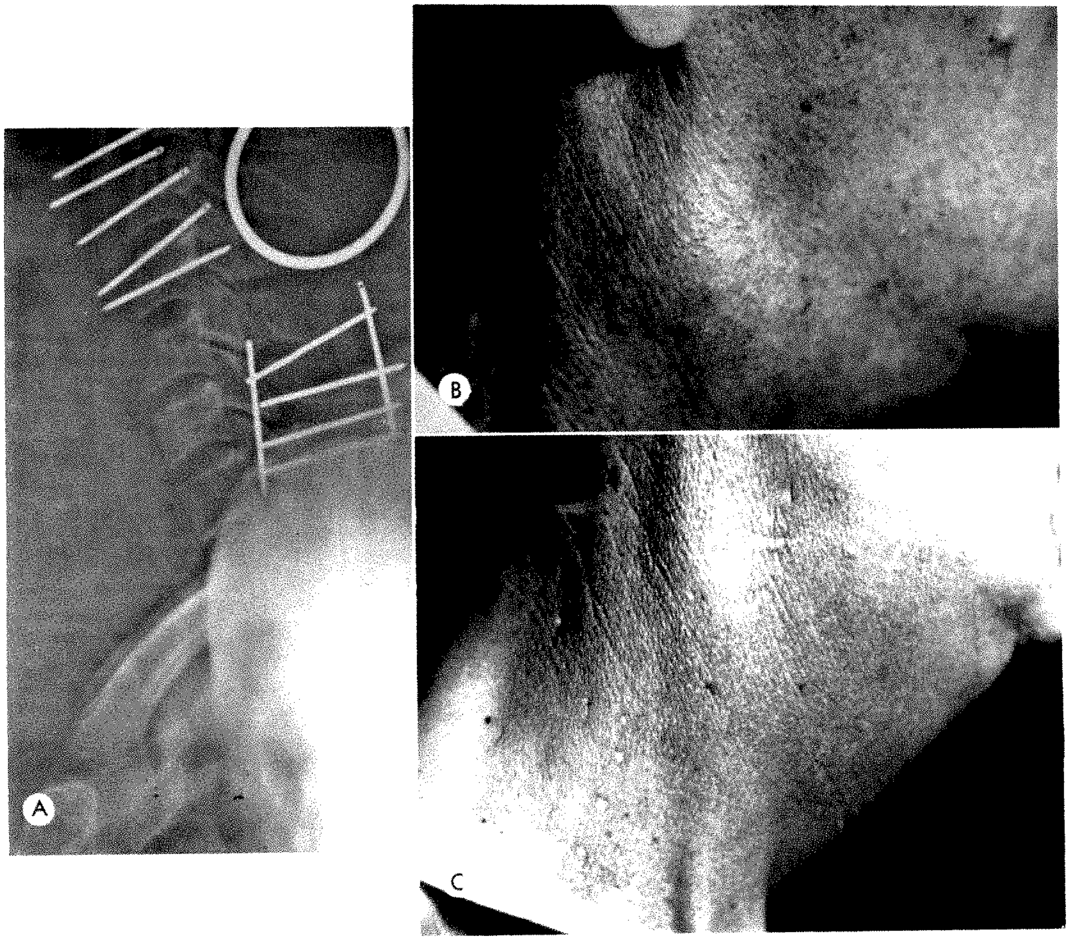

Fig. 14. W.W. 50 W M. *Squamous cell carcinoma of the right pyriform sinus with homolateral neck metastases.* The primary tumor was very extensive and the neck metastases consisted of 3 matted lymph nodes, the largest of which measured 5×7.5 cm. in diameter, situated in the upper portion of the carotid chain. Positive biopsies were obtained from both the primary lesion and the lymph nodes. The patient developed a 1.5 cm. lymph node low in the posterior triangle of the neck during treatment. Telecobalt therapy was used for the primary lesion; combined telecobalt therapy and radium implantation for the lymph nodes. The implantation was performed 2 weeks after completion of the external therapy, to include only the residual, palpable disease in the neck.

(*A*) The upper implantation was done with half-intensity needles; the lower with a typical Paterson-Parker radium arrangement. The dosage was as follows: the primary lesion received 7,000 r tumor dose in 6½ weeks by telecobalt therapy; the metastases in the upper neck received 7,500 r tumor dose in 6½ weeks by telecobalt therapy plus 1,000 r by interstitial radium. The metastases in the lower neck received 5,000 r tumor dose in 4 weeks by telecobalt therapy plus 2,500 r by the radium implantation.

(*B*) Swelling of the neck, due to metastatic lymph nodes, before treatment. (*C*) The lymph nodes in the upper carotid chain regressed completely, leaving some indurated edema of the region. The lymph nodes in the lower neck regressed partially in size to regrow 10 months later at which time a positive biopsy was obtained. A radical neck dissection was performed 1 year after treatment showing no residual disease in the upper carotid chain and a 2×3 cm. positive lymph node low in the posterior triangle of the neck. The incision healed per primam intentionem and the patient is without evidence of disease 18 months after therapy.

Comment. For small residual lymph nodes, implants using half-intensity needles are advisable to increase the dose only in the tumor area with minimal dose to the skin and other normal tissues. The sterilization of large masses of lymph node metastases in the neck is possible only by very heavy irradiation. Neck dissection after heavy irradiation is feasible without untoward complications provided the techniques of both irradiation and surgery are proper. The recurrence in the lower neck in this patient was perhaps due to the fact that this lymph node was situated too near the margin of the field of cobalt therapy and thus may have been inadequately irradiated.

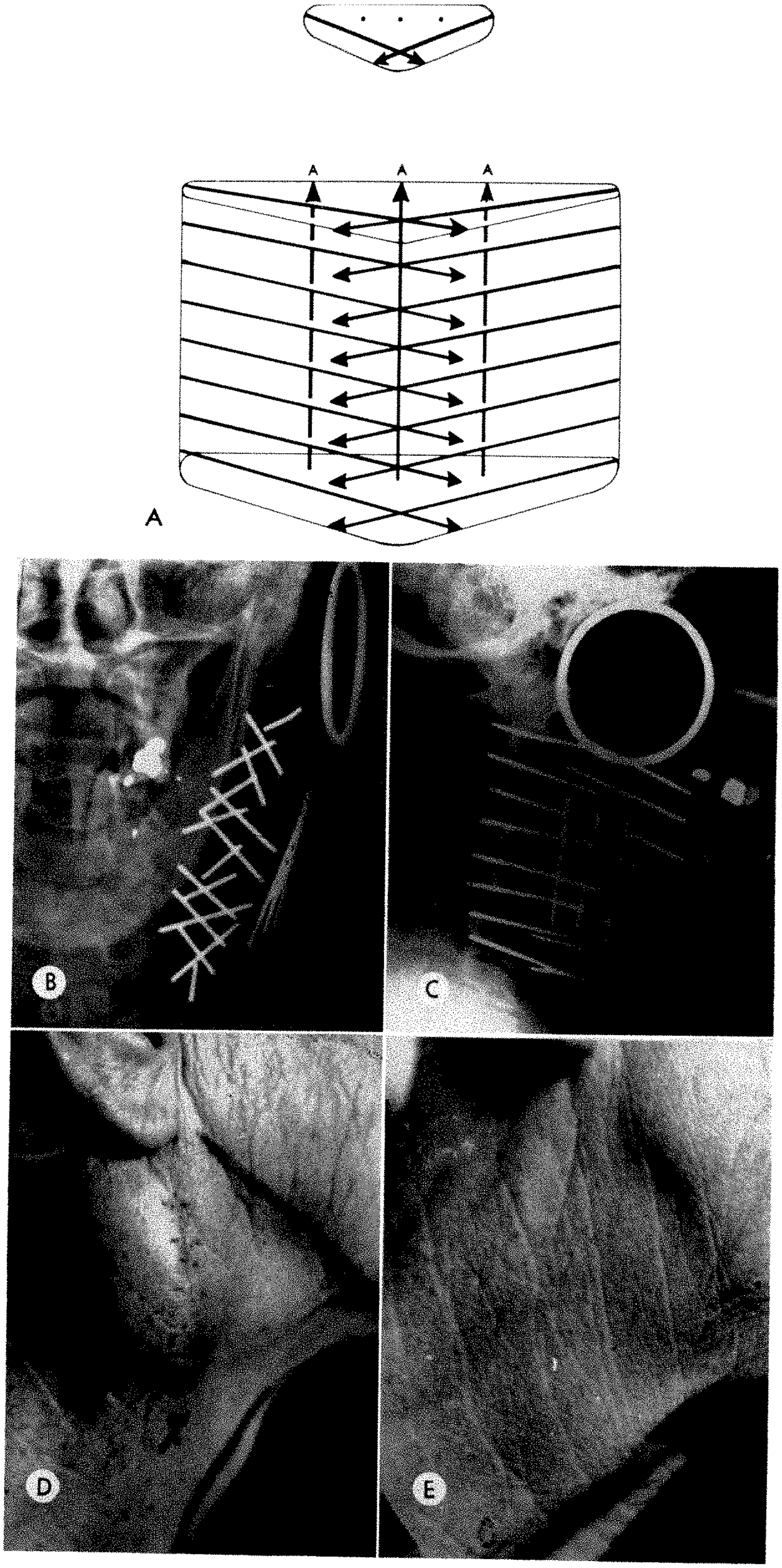

FIG. 15. H.W, 63 W F. *Metastatic squamous cell carcinoma in the lymph nodes of the right upper carotid chain proved by biopsy.* The mass was fixed and measured 5 cm. in its greatest diameter. The primary lesion on the left side of the soft palate was treated by surgical excision 9 months previously and was under control. A combined technique of telecobalt therapy and interstitial radium was used. The telecobalt therapy with anterior and posterior tangential fields included the entire right side of the neck.

(*A*, *B* and *C*) The radium implant consisted of a triangular, 3 plane arrangement of half-intensity needles without crossing. This pattern is best suited for irradiation of large masses in the neck with minimal damage to the skin since the dose is very uniform within the implant. In the present case the dose was 5,000 r tumor dose in 4 weeks by telecobalt therapy and 2,500 r in 55 hours by interstitial radium.

(*D*) Swelling of the neck due to metastatic lymph node involvement before treatment. (*E*) The treatment was very well tolerated. The patient is free of disease 1 year after therapy.

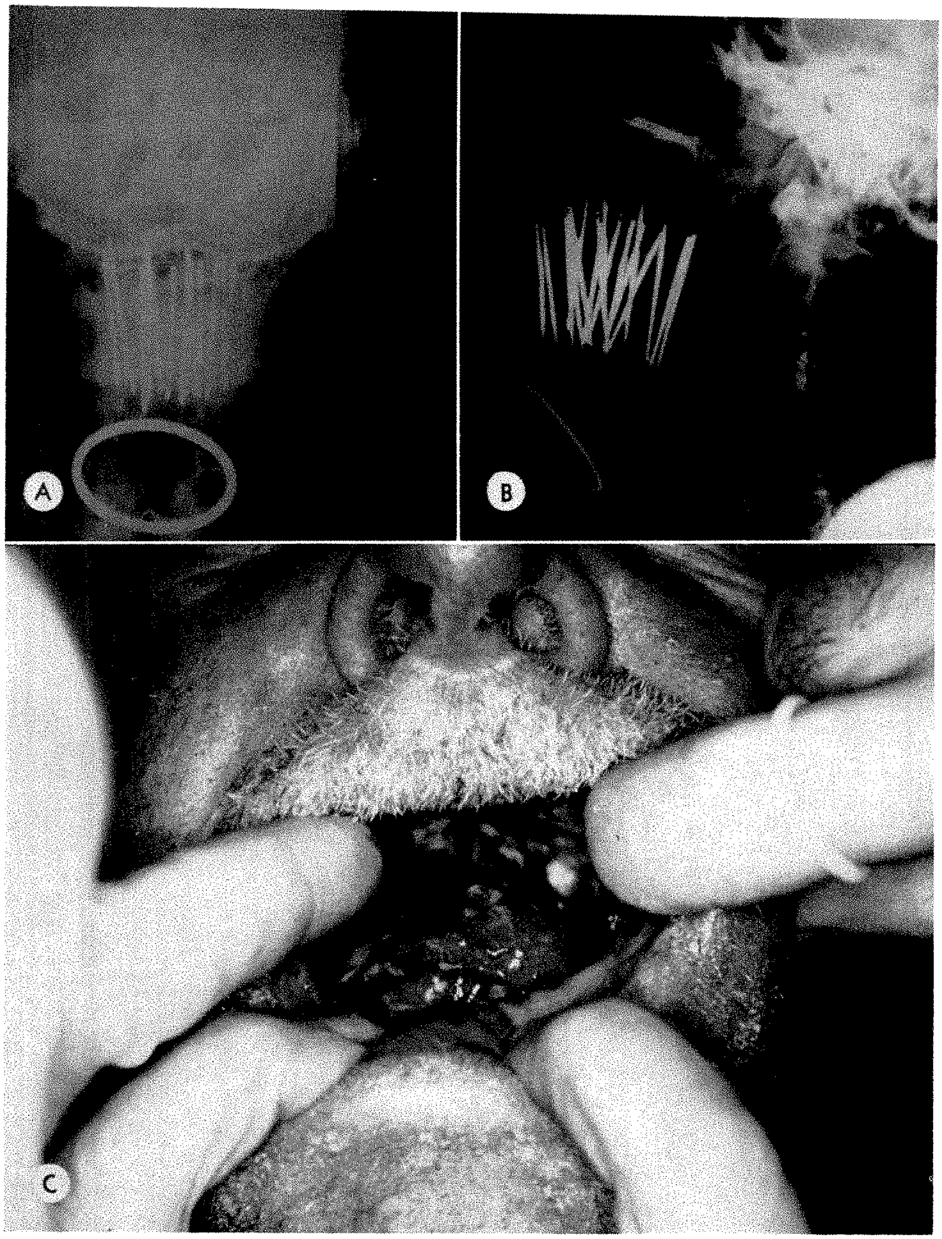

Fig. 16. H.L. 66 W M. *Squamous cell carcinoma involving the whole of the anterior two-thirds of the tongue with invasion of both sides of the floor of the mouth.* The root of the tongue was deeply infiltrated by tumor. No lymph nodes were palpable in the neck. Combined telecobalt therapy and interstitial radium was used rather than implantation alone because of the extent of the disease and its proximity to the bone.

(*A* and *B*) The implant was a simple volume implant which included the whole tongue and floor of the mouth. The dose was 4,000 r tumor dose in 4 weeks by telecobalt therapy and 3,500 r in 54 hours by interstitial radium.

(*C*) Lesion before treatment which was well tolerated. The patient obtained partial regression of the lesion but it started to regrow after 4 months.

Comment. In our experience, it has been difficult to obtain even temporary control of this type of massive tumor of the tongue by any radiation technique.

voltage is used, an effort is made to remain at a maximum dose of 6,000 r in the subcutaneous tissues of the entrance field in order to avoid delayed changes with consequent deep fibrosis and sometimes necrosis as have been described in patients treated several years ago with high doses of supervoltage irradiation.

The proportion of the total tumor dose delivered by the external and interstitial irradiation varies with the type of combination used. We have been using the following

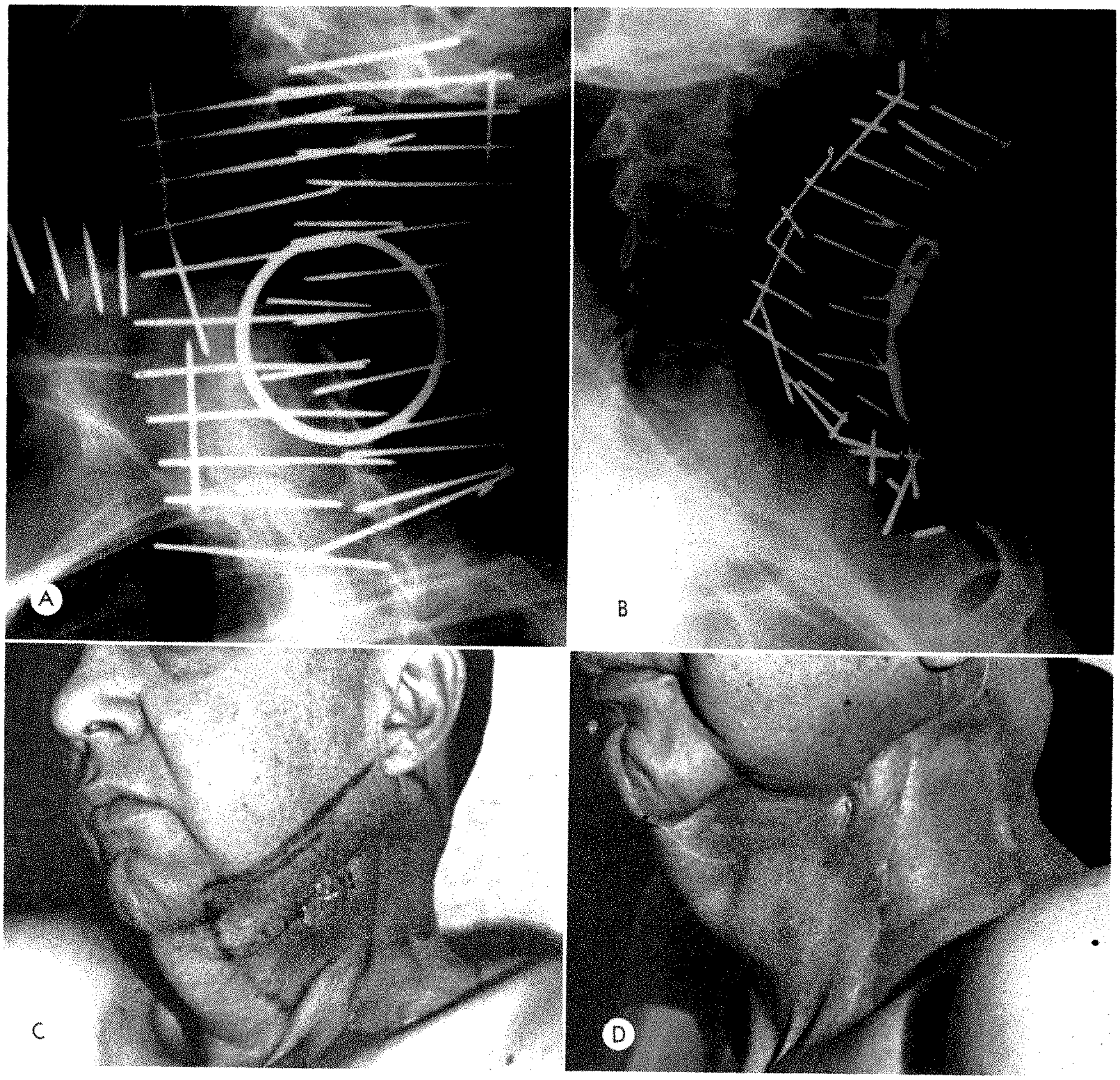

Fig. 17. D.S. 54 W M. *Extensive recurrent squamous cell carcinoma of the left side of the neck.* The primary lesion of the lateral border of the tongue was treated by surgery one year previously and was under control. At the time of the operation a commando procedure was performed with a radical neck dissection. Tumor was known to be left attached to the carotid bulb. The "recurrence" involved the whole left side of the neck with a shell-like subcutaneous infiltration which was not over 1 cm. thick in most of its extensions. It was decided to use a combined procedure of telecobalt therapy and interstitial radium. The telecobalt therapy with a single field covered an area extending from the mastoid to the clavicle.

(*A* and *B*) The interstitial radium application consisted of a single plane implant following the Paterson-Parker rules of distribution. A dose of 3,000 r tumor dose was delivered in 3 weeks by telecobalt therapy. The radium implant delivered 4,000 r in 58 hours and followed the external irradiation without interval.

(*C*) Extent of lesion before treatment. (*D*) The treatment was well tolerated. The local control of the disease was good, and the treated area remained free of disease even though the paitient died 18 months later because of distant metastases.

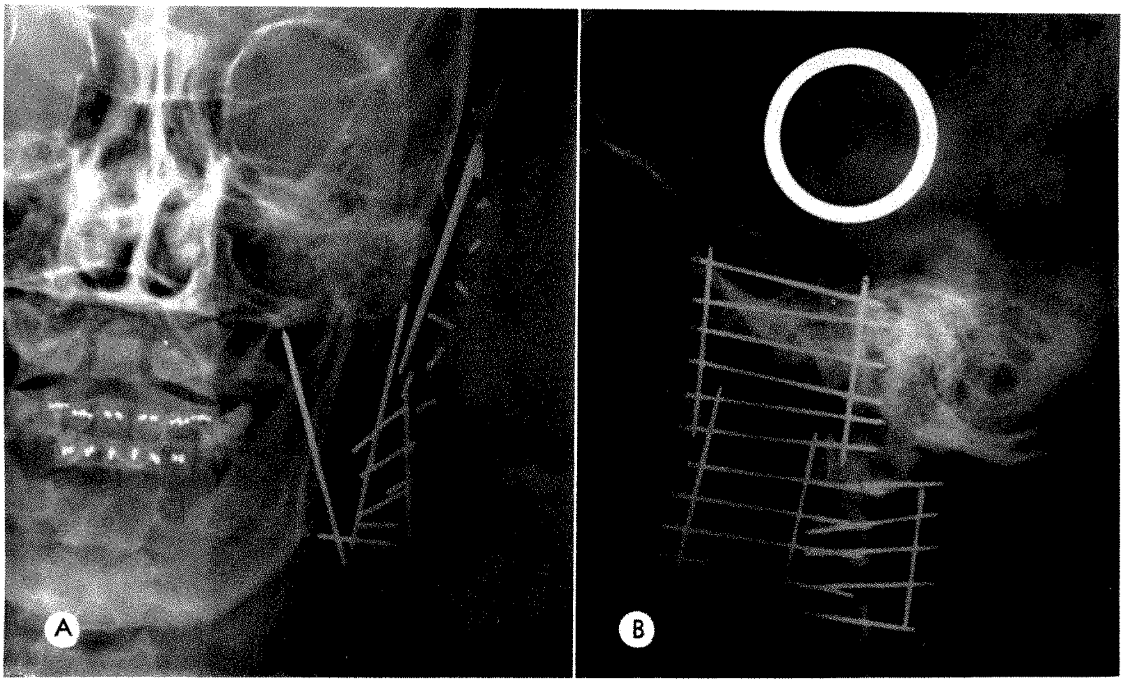

FIG. 18. *Parotid implant.* In most cases of inoperable malignant tumors of the parotid gland or postsurgical recurrences, we prefer to use interstitial radium therapy. An exception is made in cases of very large tumors where a proper implant is not feasible at the beginning.

Treatment. The implant has been described in a previous paper (F.B.[1]). The extension of the deep portion of the implant is determined by the position of the tumor. The upper neck is included so as to irradiate the lymph nodes most commonly involved (carotid chain). The postoperative implants are performed 2 weeks after the operation (see example below); if performed earlier, there is interference with the wound healing. In most of the postoperative recurrences, the tumor is multiple but of small volume. Thus, a radium implant alone is the treatment of choice. In cases with bulky tumors, a combined approach with telecobalt therapy and interstitial radium is generally indicated.

Dosage. For postoperative treatment we try to deliver 6,000 to 7,000 r in 6 to 7 days at 0.5 cm. from each plane. When tumor is present, we deliver from 8,000 to 8,500 r at the site of the tumor and 6,000 to 7,000 r to the rest of the treated area at the same time. If combined therapy is used, 3,000 to 4,000 r will be delivered prior to the implantation in 2 to 3 weeks and the rest, up to the previous doses, by the implant. This has proved to be well tolerated by all the patients, with a minimum of immediate and late radiation reactions and without a resulting "dry mouth."

S.A. 36 W M received postoperative treatment for a malignant mucoepidermoid carcinoma. The original tumor was 3 cm. in diameter, located in the upper portion of the superficial parotid lobe.

(*A* and *B*) The aim of the implantation was to cover mainly the superficial portion of the parotid, and 7,000 r was delivered in 150 hours. The reaction was very slight.

• The patient is free of disease 2 years after therapy, showing only slight radiation changes.

ranges of dosage which should be modified according to each particular case:

GROUP 1. Full radical treatment with external irradiation (cobalt teletherapy) followed by 1,000 to 2,000 r delivered by interstitial irradiation to the core of the residual tumor.

GROUP 2. (a) Initially, 2,000–3,000 r tumor dose by external irradiation, or whatever amount is necessary to produce the desired shrinkage of the tumor. The interstitial treatment then delivers the dose necessary to arrive at a total of 6,500 to 7,000 r in all. In very large tumors, an additional 500 to 700 r is delivered to the core of the tumor by leaving in the necessary group of needles the required extra time.

(b) No definite dosage can be assessed in this group as the different proportions depend upon the dose which had been delivered by the radium prior to its removal. However, a total of 6,500 r is seldom to be exceeded as the tolerance of the tissue to a combined procedure is less than when radium is used alone, due to the increased volume of tissue being irradiated.

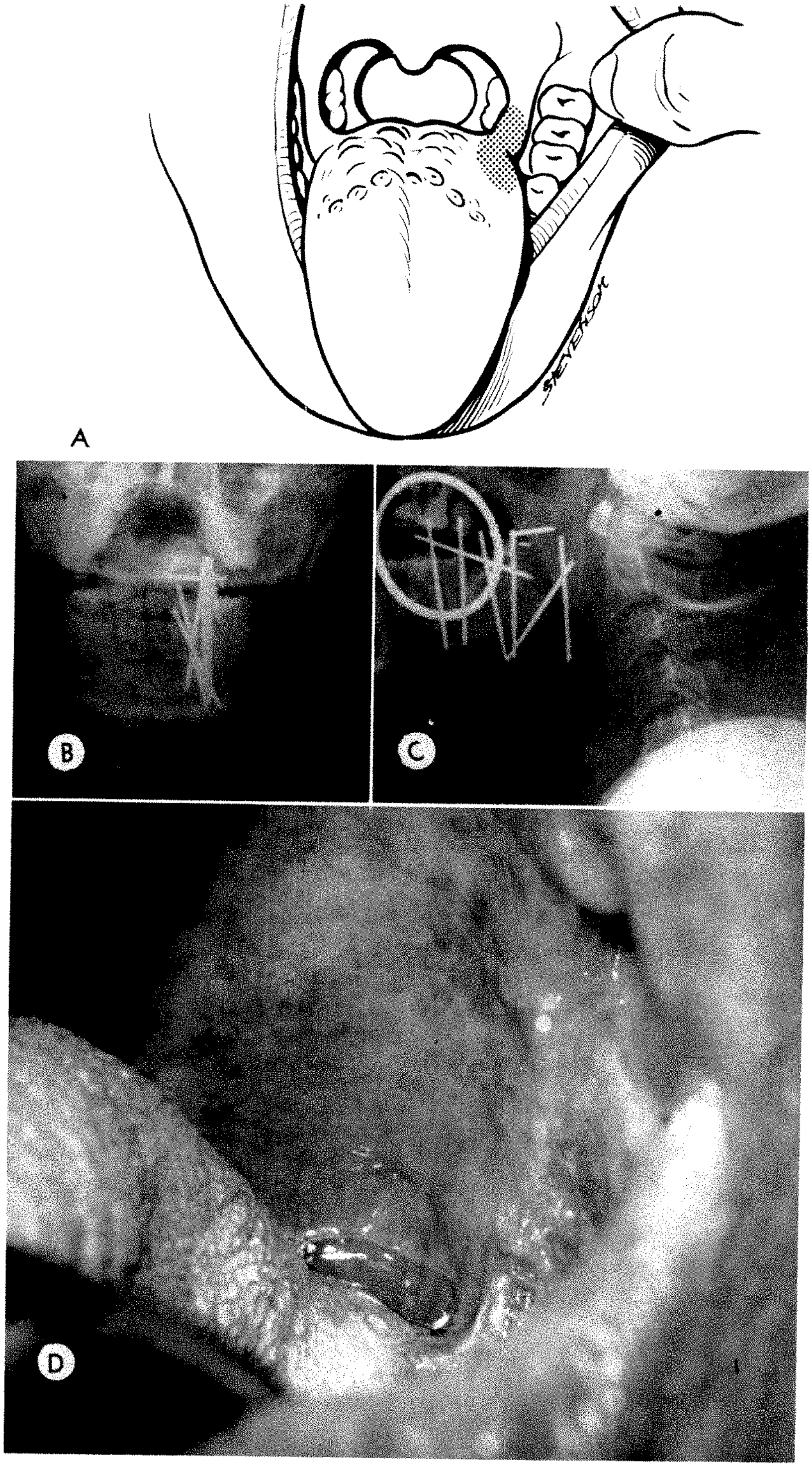

FIG. 19. L.F. 57 N F. *Squamous cell carcinoma of the palatoglossal fold with a small extension into the tongue.* No lymph nodes were palpable in the neck.

(*A*) Sketch of the lesion. It was decided to treat this lesion with interstitial radium alone.

(*B* and *C*) An implant of the single plane type was used in the most posterior portion of the lateral aspect of the tongue with one additional needle in each faucial pillar (anterior and posterior). The crossing needles were inserted in the tongue and in the soft palate. Silver clips were placed to mark the position of the lesion in relation to the implant. The roentgenograms taken of the implant showed it to be unsatisfactory as the lesion was covered only by the superior edge of the implant. The radium was removed and treatment was completed by telecobalt using a single small field. The interstitial treatment was useful in raising the dose from the medial aspect. The implant delivered 1,000 r to the lesion and the external irradiation 5,000 r tumor dose in 4 weeks.

(*D*) The reaction was mild. The patient is alive with no evidence of disease 3 years later showing no radiation changes in the mouth.

Comment. If an implant is not satisfactory, it should be removed without hesitation.

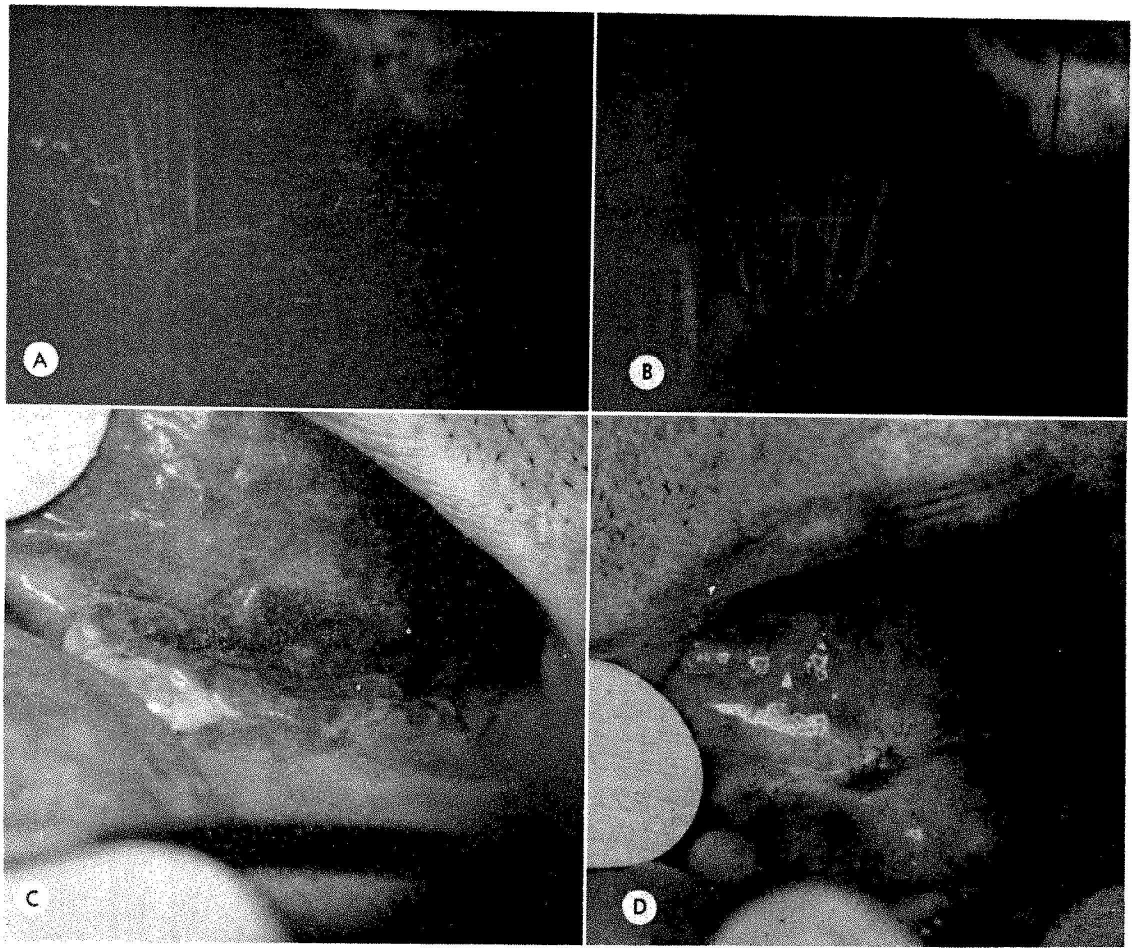

FIG. 20. B.R. 57 W M. *Squamous cell carcinoma of the left side of the floor of the mouth, ulcerated and infiltrating.* A 1 cm. lymph node was palpable in the submaxillary area. Interstitial treatment with radium was indicated.

(*A* and *B*) A double implant was used: a volume implant through the tongue covering the whole lesion, and a submaxillary single plane implant of full-intensity needles. The lesion was tagged with silver clips. The patient was restless and developed progressive edema and a hematoma of the tongue. On the third day a repeat roentgenogram showed marked displacement of the tongue needles upward; the silver clips were now at the lower end of the needles indicating inadequate coverage of the lesion. The implant was removed and treatment was completed with telecobalt therapy. The radium implant delivered 3,100 r in 72 hours and the telecobalt therapy 4,000 r tumor dose in 3 weeks. The duration of the treatment was 4 weeks.

(*C*) Lesion before treatment. (*D*) The lesion regressed completely but recurred 1 year later. A commando-type of operation was performed, and, presently, 2½ years after the first treatment, the patient is free of disease

GROUP 3. Generally, half of the total dosage is delivered by the external irradiation and half by the interstitial irradiation, here again not exceeding a total of 6,500 r except in cases of very large tumors or in some adenocarcinomas where an extra dose (up to 1,000 r) is delivered to the core of the tumor.

COMMENT

The procedure of combined therapy is particularly useful in centers where supervoltage therapy is not available. In many lesions of the oral cavity and oropharynx, it is difficult and often even impossible to deliver a lethal tumor dose by external irradiation alone without overtaxing the skin, particularly in cases of well-differentiated large squamous cell carcinomas or adenocarcinomas. The addition of interstitial therapy may offer the only possibility of achieving a therapeutically significant dose. This is particularly true in lesions of

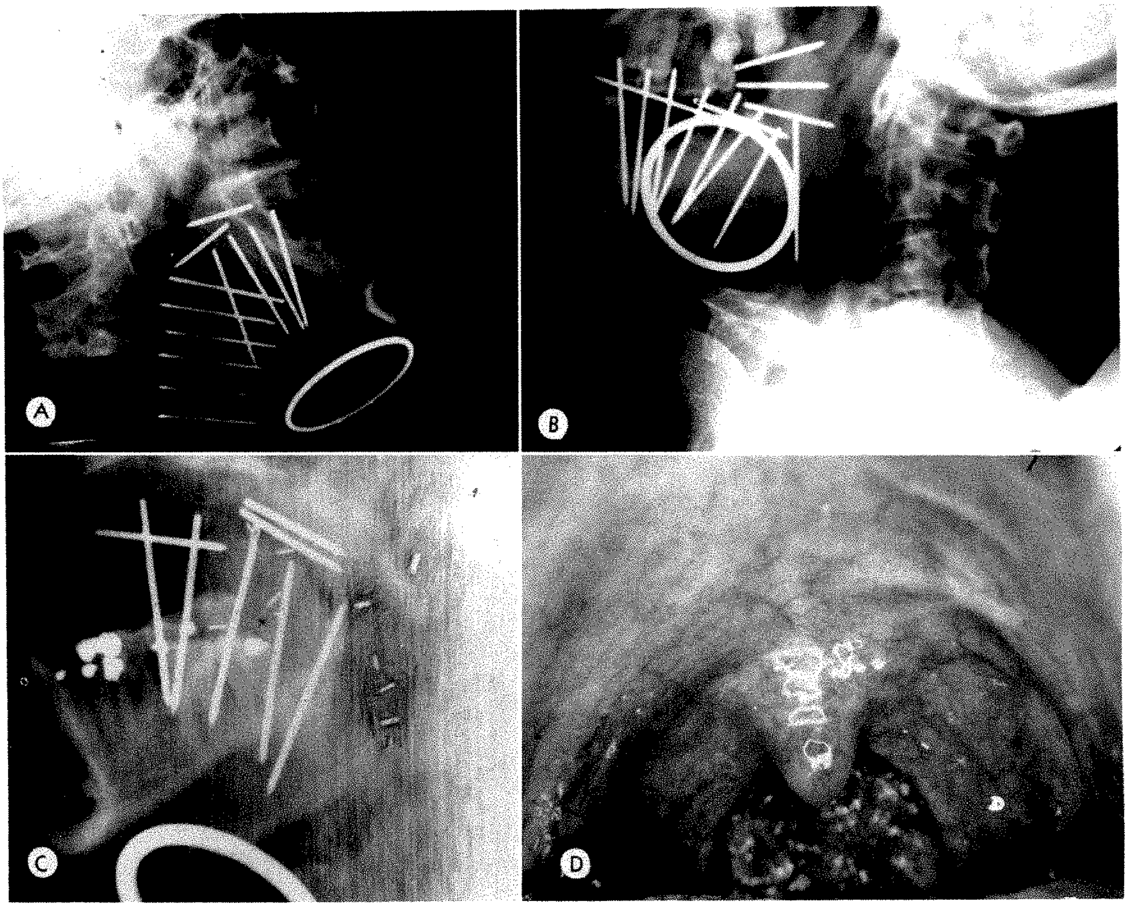

Fig. 21. *Tonsillar and peritonsillar tumors* (true tonsillar, palatoglossal and glossotonsillar areas, and faucial pillars). This is an important group of tumors for combined therapy because they occur relatively frequently and since they are laterally placed they are well suited for the technique described. The external beam portion of the irradiation is, in general, the same for all cases: a single field covering the tumor and its extension, actual or potential. In cases with a large transverse diameter or with the tumor approaching the midline, 2 parallel-opposing fields are used, generally with differential loading (2:1 in favor of the diseased side). This arrangement is chiefly used when only conventional therapy is available. The interstitial therapy will vary depending upon the original site of the tumor and its extensions. The following are the types of implants commonly used:

(*A*) For very early lesions of the anterior pillar, palatoglossal sulcus with or without extension to the proximal portion of the soft palate, we use an implant as shown in *A*. The crossing needles are generally shared between tongue and soft palate. The neck portion is added only if lymph node metastases are present.

(*B*) For extensive lesions of the previous group and especially for tumors of the glossotonsillar area which (usually) have a large extension into the tongue, implants as shown in *B* are used. The portion of the implant in the tongue or soft palate will vary according to the extent of the tumor. Very often a double plane is necessary for the tongue implant. The most posterior needle is inserted in the anterior pillar. Whenever necessary, some additional needles or seeds are implanted in the posterior pillar, buccinator area, retromolar trigone, or buccal mucosa.

(*C*) For the true tonsillar lesions or for the rare posterior pillar tumors, the implant should project more posteriorly due to the common extension of the disease in this direction. We have tried to extend the implant with radium needles, but they were difficult to place and more difficult to keep in the correct position. Presently we implant gold or radon seeds in 1 or 2 rows as needed; 1 row in the posterior pillar and the second in the angle formed between the posterior and lateral walls of the oropharynx as shown in *C*.

Dosimetry. For early tumors we deliver 3,000 r tumor dose in 2 to 3 weeks by telecobalt or conventional beam therapy, and 3,500 r with interstitial radium. For more advanced tumors the dosage has been 3,500 to 4,000 r tumor dose in 3 to 4 weeks with external therapy and 3,000 to 3,500 r with interstitial therapy.

(*D*) The acute reaction produced by this type of treatment is very well tolerated, and the late changes are minimal. The most salient feature is the conservation of the mouth moisture as shown in *D*, a patient treated as described 3 years previously for a squamous cell carcinoma of the tonsil.

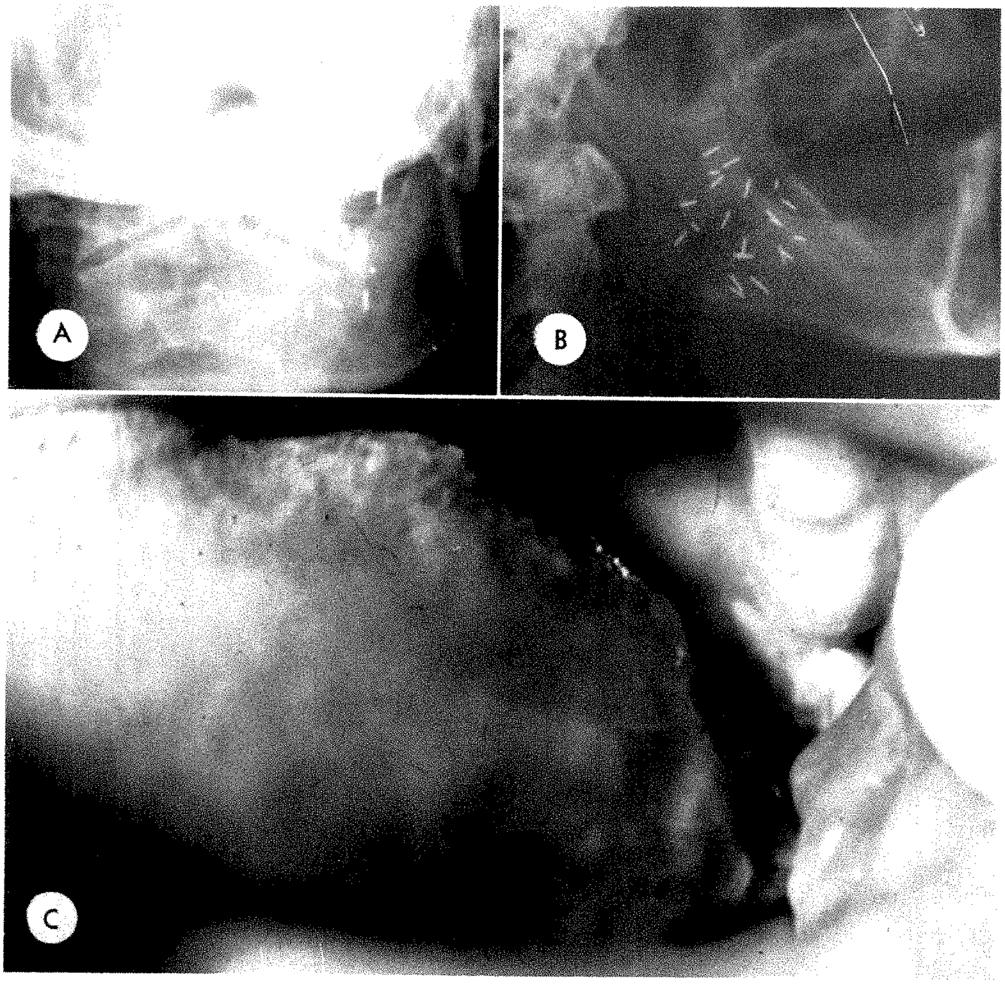

Fig. 22. A.K. 69 W M. *Squamous cell carcinoma of the left buccinator sulcus, with extension to the buccal mucosa, retrom trigone and soft palate.* The lesion was deeply infiltrating with a necrotic base. No lymph nodes were palpable. A combi treatment by telecobalt therapy and radon seed implantation was planned. The external irradiation was delivered thro a single field.

(*A* and *B*) The implant with radon seeds was of a single plane pattern, following Paterson-Parker distribution. seeds were inserted in the lateral aspect of the tongue, soft palate, and anterior buccal mucosa and retromolar trigo The dose was: telecobalt therapy: minimum of 4,400 r tumor dose in 4 weeks; radon implant: 2,000 r at 1 cm. from plane of seeds.

(*C*) Lesion before treatment. The patient developed a rather brisk, slowly regressing mucositis. The ulceration the area of disease took 8 months to heal. Repeated biopsies showed it to be free of tumor. The patient died of a card vascular accident 18 months after treatment, free of tumor.

the base of the tongue, peritonsillar and tonsillar tumors, and extensive lesions of the floor of the mouth with invasion of the gum and of the retromolar trigone. In laterally placed lesions this is a better technique than using a single field or two parallel opposing fields with external beam therapy.

In centers where supervoltage therapy is available, it is not an indispensable method of treatment, but it is no doubt a mo rational technique and one which is clos to that ideal of radiation therapy whi seeks for specific irradiation of the tum bearing tissues.

It is very gratifying to see that patien treated by this combined approach, esp cially those in Group 3, have a greatly im proved tolerance to the treatment. Th outstanding feature is best demonstrated

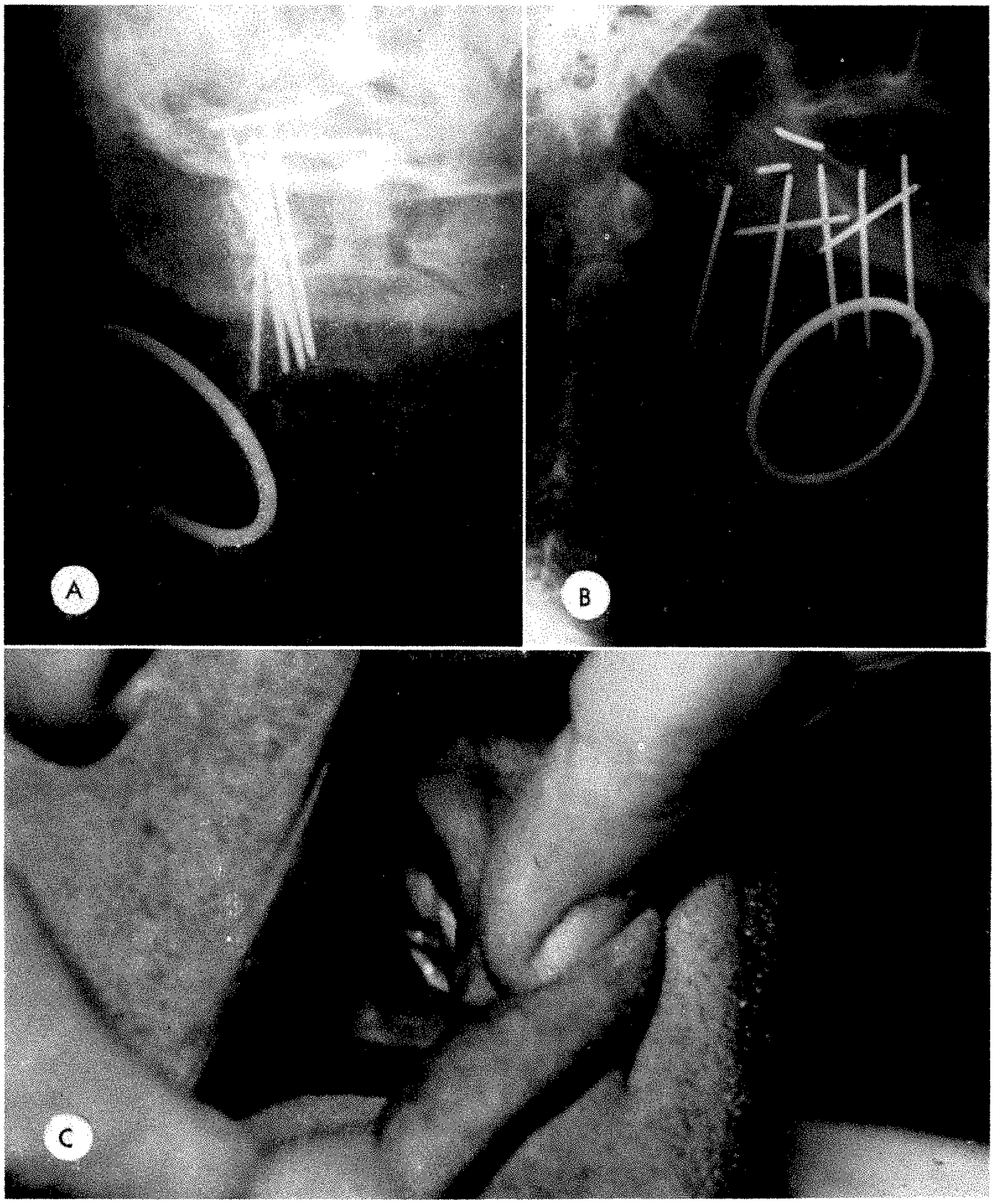

Fig. 23. L.R. 45 W M. *Squamous cell carcinoma of the most posterior portion of the medial aspect of the left lower gum, attached to bone without invasion of it.* A combined technique of 220 kv. roentgen rays, single field, and single plane radium implant was used.

(*A* and *B*) The implantation was performed in the most posterior portion of the lateral aspect of the tongue opposite the lesion. Two additional full-intensity needles were inserted in the soft palate to cover an extension of the tumor. With 220 kv. roentgen rays, a tumor dose of 2,000 r was delivered in 2 weeks. With the implant, 5,500 r was delivered at 0.5 cm. and 3,000 r at 1 cm. in 104 hours.

(*C*) Lesion before treatment. One year after treatment a necrotic ulcer developed in the lower gum with bone necrosis. Partial mandibulectomy was performed 2 years after treatment with complete healing. The patient is free of disease 4 years after therapy.

Comment. This was our first patient treated by a combined approach; the dose was probably too high and the treatment insufficiently protracted.

the follow-up where marked difference can be appreciated in late changes; the mouth remains moist and the skin and mucosal changes are minimal.

The sources of irradiation used in our cases have been either radium needles, radon seeds or a combination of both, depending upon the anatomic site of the lesion. In tonsillar or peritonsillar tumors, the posterior portion of the area (posterior pillar, lateral and posterior pharyngeal walls) is implanted with radon or gold seeds because of the difficulty in keeping needles in place in this region; the remainder of the implantation is performed with needles in the lateral portion of the tongue. The crossing needles are implanted in the tongue and soft palate.

The dose levels must be carefully planned and calculated. The ones we suggest are considered safe. In our first group, in which we tried to deliver a total dose of 7,000 r or more, the incidence of necrosis was high.

The cure rate so far obtained has been very promising, and, in some patients who developed a second primary lesion within the oral cavity or elsewhere in the head and neck, a second treatment by radiation has been possible without untoward consequences.

SUMMARY

A combined technique of treatment of head and neck tumors by external beam and interstitial therapy is described. The main advantage of this technique is that the volume of tissue irradiated to a high dose is reduced. This combination is possible in three different ways: (1) interstitial gamma therapy used as a complement of external beam therapy; (2) external beam therapy used as a complement of interstitial radium therapy; and (3) external beam therapy and interstitial irradiation used as agents of equal importance.

The main indications and usual doses delivered by this procedure are given. Combined therapy is very useful in centers where only conventional therapy is available, but, even in centers where supervoltage therapy is in use, this treatment offers a better solution to many problems. The immediate and late reactions to the treatment are diminished.

It is possible that by such a planned technique the results in some cases of head and neck tumors could be improved and the side effects and complications diminished.

Details of techniques, dosimetry, indications and examples are given.

PART IV. UNUSUAL RADIUM IMPLANTS IN THE TREATMENT OF CANCER

One of the main objections to interstitial gamma-ray therapy already mentioned is the lack of versatility allowed by this technique. It is granted that its applications are limited, for many radiosensitive tumors do not lend themselves to treatment by interstitial therapy. Some of the contraindications conventionally accepted are: (1) large volume or very anaplastic tumors; (2) inaccessible areas; and (3) lesions close to or involving bone or cartilage.

There are patients with tumors of the well-differentiated group (squamous cell or adenocarcinoma) in whom treatment by external irradiation is difficult because a large volume of normal tissue must be irradiated in order to reach the tumor, because it is impossible to avoid irradiation of sensitive structures or because it is difficult to get enough dose at the depth of the tumor. Some of these cases can be satisfactorily treated by interstitial therapy.

It is our intention to demonstrate that a wider use of interstitial therapy is possible, even under unusual circumstances to the benefit of some patients who would pose difficult problems of technique if they were to be treated with external beam therapy alone.

Implants may be termed unusual when they are placed:

1. *Through bone or cartilage.* It is often stated that radium implantation through or near bone or cartilage is fraught with a very high incidence of necrosis and, therefore, should be avoided. Our experience, over more than a seven year period in treating a

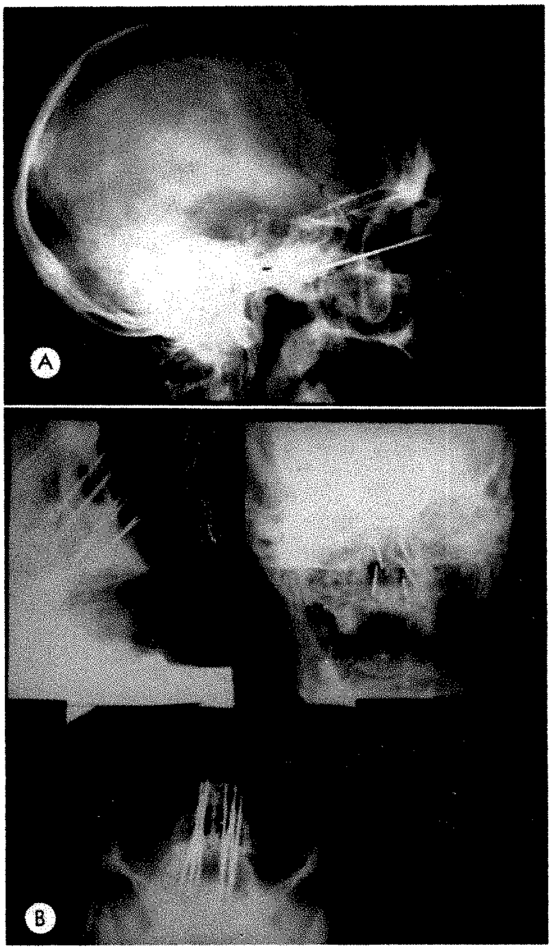

Fig. 24. *Ethmoid implant.* (*A* and *B*) This is a double plane implant, which is a modification of the single plane implant as developed by Dobbie in Manchester. It is felt that this modification enlarges the area irradiated without increasing the dose close to the implant to dangerous levels. It is indicated in cases of early squamous cell carcinoma of the nasal septum, in cases of esthesioneuroepithelioma as a complement of external irradiation in extensive tumors of the ethmoid, and in postoperative ethmoidal recurrences after combined surgical and radiation therapy of maxillary antrum tumors. It must be realized that the indications for radium alone must be precise and that only small well-differentiated tumors can be so treated.

Treatment technique. The implant is always of a double-plane pattern using crossing at the outer end, or dumb-bell or Indian club type needles, depending upon the site of the primary lesion in relation to the surface. In general, the separation between planes is 2 cm. The day prior to the implantation a roentgenogram is taken with a straight wire placed on the lateral aspect of the face, directed from the top of the bridge of the nose to the upper edge of the tragus. This generally follows the base of the skull as shown in *A*. The skin is marked with a line following this direction. This line is used during the implantation as a landmark, and the needles are implanted parallel to it. The implantation is started with the upper two needles which, in general, are placed on both sides of the bridge of the nose in the orbits, through soft tissues, above the level of the cribriform plate. A portable roentgenogram is taken to see if the position of the first needles is satisfactory; if it is, the whole implantation is performed parallel to these needles, boring the nasal bones with a drill whenever the implantation is done through bone. Dummy needles (made of stainless steel wire) are used during the whole procedure, and, if their position is satisfactory, they are replaced by the radium implant at the end of the procedure.

Dosage. If the treatment consists of interstitial therapy alone, we deliver a maximum of 7,000 r and a minimum of 5,000 to 5,500 r for squamous cell carcinomas. If it is to be complemented by external irradiation, the dose will vary with the particular case. The treatment was well tolerated in more than 10 cases so managed. *B* shows a patient of very advanced age (82 years old) with a small squamous cell carcinoma of the nasal septum, which is marked by silver clips.

considerable number of cases, does not bear out this statement. Bone and cartilage will tolerate an implant well, provided a uniform distribution of the sources is obtained and proper dosimetry is used. More than a score of patients so treated have had several years of follow-up without a single complication. Therefore, the proximity of bone or cartilage is not a valid contraindication to interstitial therapy (Fig. 24, 25, 26, 27 and 28).

2. *In anatomic sites which are not commonly implanted with or without complex arrangement of the radium sources.* The perineum, groin and pubis are areas where postoperative recurrences are not infrequent after the treatment of tumors originating in the vulva, penis, bladder and rectum. They manifest themselves as cutaneous or subcutaneous masses, often multiple, in the operative field and probably represent seeding of the tumor as a result of surgical manipulation. Some of these may be controlled by proper radiation therapy (Fig. 29, 30 and 31). These lesions are difficult to manage by external irradiation alone unless a large volume of tissue is irradiated, in which case a cancerocidal dose may not be tolerated. Some of these tumors are adenocarcinomas requiring very high doses for sterilization.

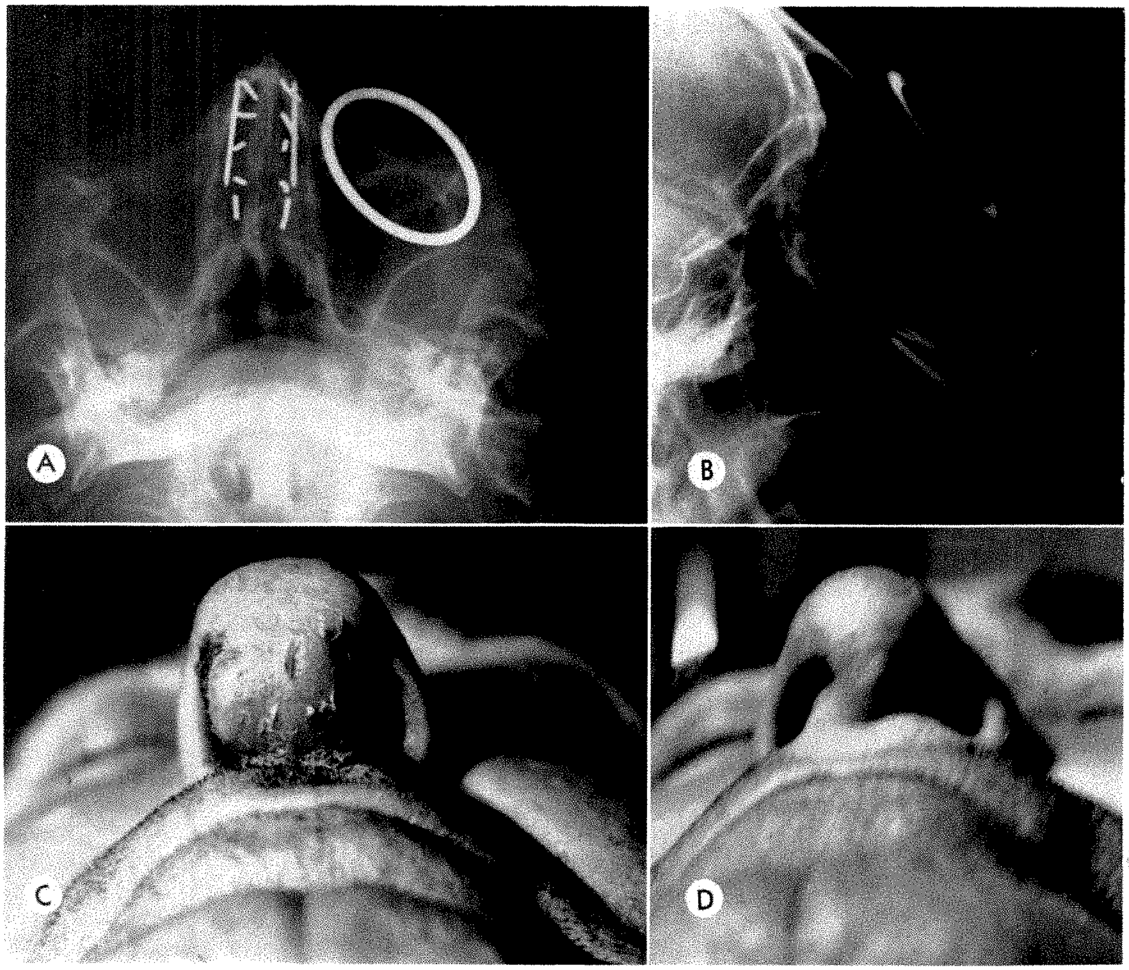

Fig. 25. A.K. 60 W M. *Squamous cell carcinoma of the columella involving the lower portion of the nasal septum, the tip of the nose, and the medial portion of both alae nasi.* It was decided to use interstitial radium alone.

(*A* and *B*) A double-plane implantation was performed. Crossing needles were used at the outer ends of the planes. Most of the needles went through cartilage. The dose delivered was estimated as a maximum of 6,500 r and a minimum of 5,600 r. The treatment time was 112 hours.

(*C*) Lesion before treatment. (*D*) The treatment was very well tolerated. A good cosmetic result was obtained. The patient has been free of disease for 18 months.

3. *In surgically exposed areas.* The classic indications for interstitial gamma-ray therapy can be considerably enlarged if enough ingenuity is used in devising proper geometric arrangements of the radiation sources and by making some lesions accessible by surgical procedures, such as: episiotomy, pharyngotomy, cystotomy, laparotomy, etc. These are cases where interstitial radiation through a surgical incision can solve a difficult therapeutic problem. It is common practice in the treatment of carcinoma of the bladder. Figure 32 is an example of residual disease in the bladder after roentgen-ray therapy, treated in this manner. This technique may also be indicated in some exceptional cases of tumors ordinarily considered inaccessible, *i.e.*, pelvic tumors through a colpotomy (Fig. 33) or some residual or recurrent tumors of the posterior wall of the pharynx through a lateral pharyngostomy.

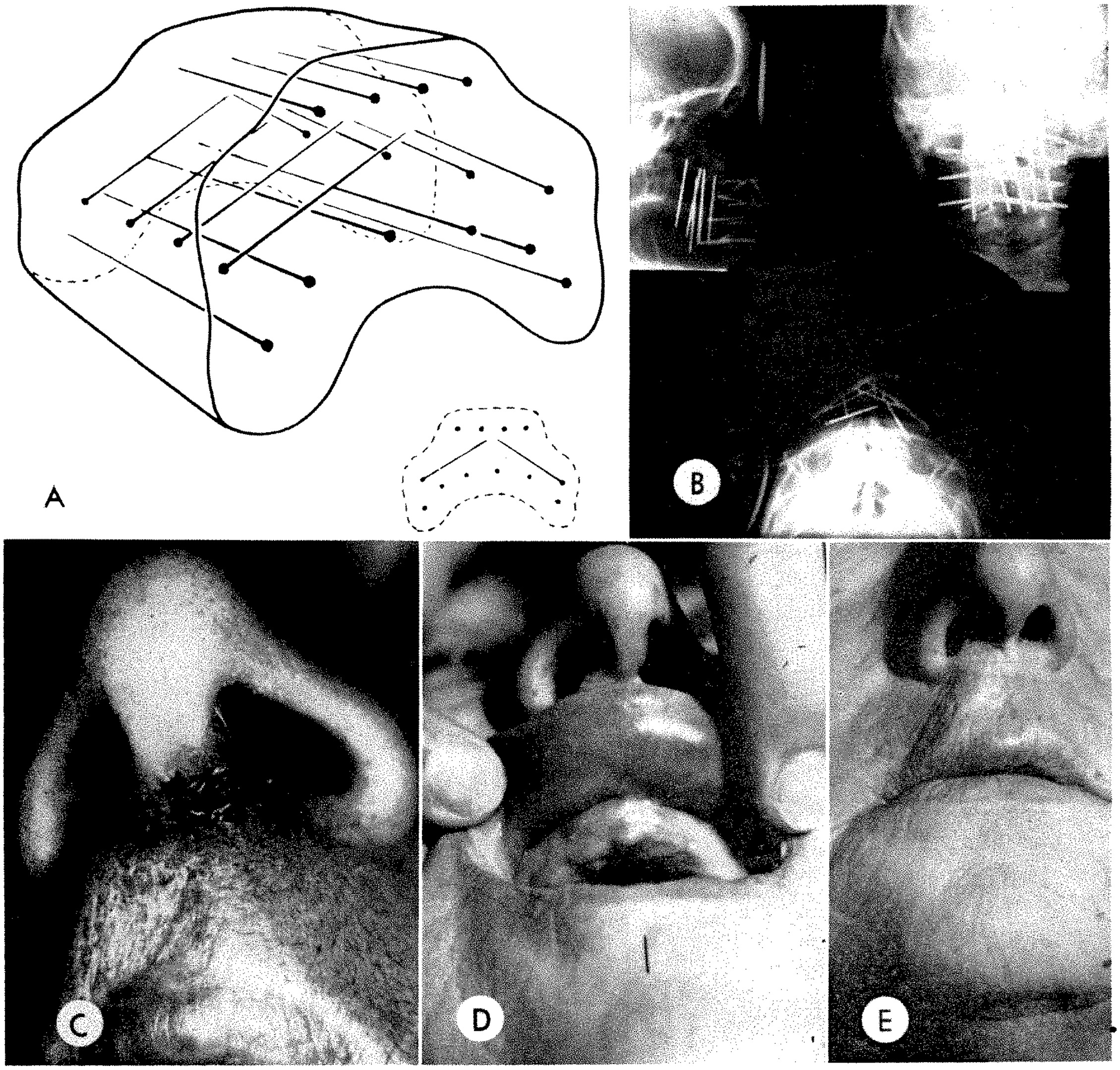

FIG. 26. E.E. 64 W F. *Squamous cell carcinoma originating in the columella involving the lower portion of the nasal septum, both alae nasi, upper lip in its whole thickness, and the upper gingivolabial sulcus.* No lymph node metastases were palpable. It was decided to use interstitial radium alone, complex pattern type.

(*A* and *B*) The implant consisted of 3 planes of radium needles. The deepest plane was implanted through the bone of the upper alveolar ridge, behind the tumor; the middle plane was inserted through the upper lip and included both alae nasi. The superficial plane was implanted in the dorsum of the nose. The last two planes went through or very near cartilage. A very uniform volume of irradiation was obtained, as shown in *A*. The estimated dose was 5,400 r delivered in 100 hours.

(*C*) Lesion before treatment. The treatment was very well tolerated. The mucositis in the nose was confluent and a wax mold was kept in each nasal cavity for 3 weeks in order to prevent adhesions. (*D* and *E*) The therapeutic and cosmetic results were excellent. The patient is free of disease after 18 months.

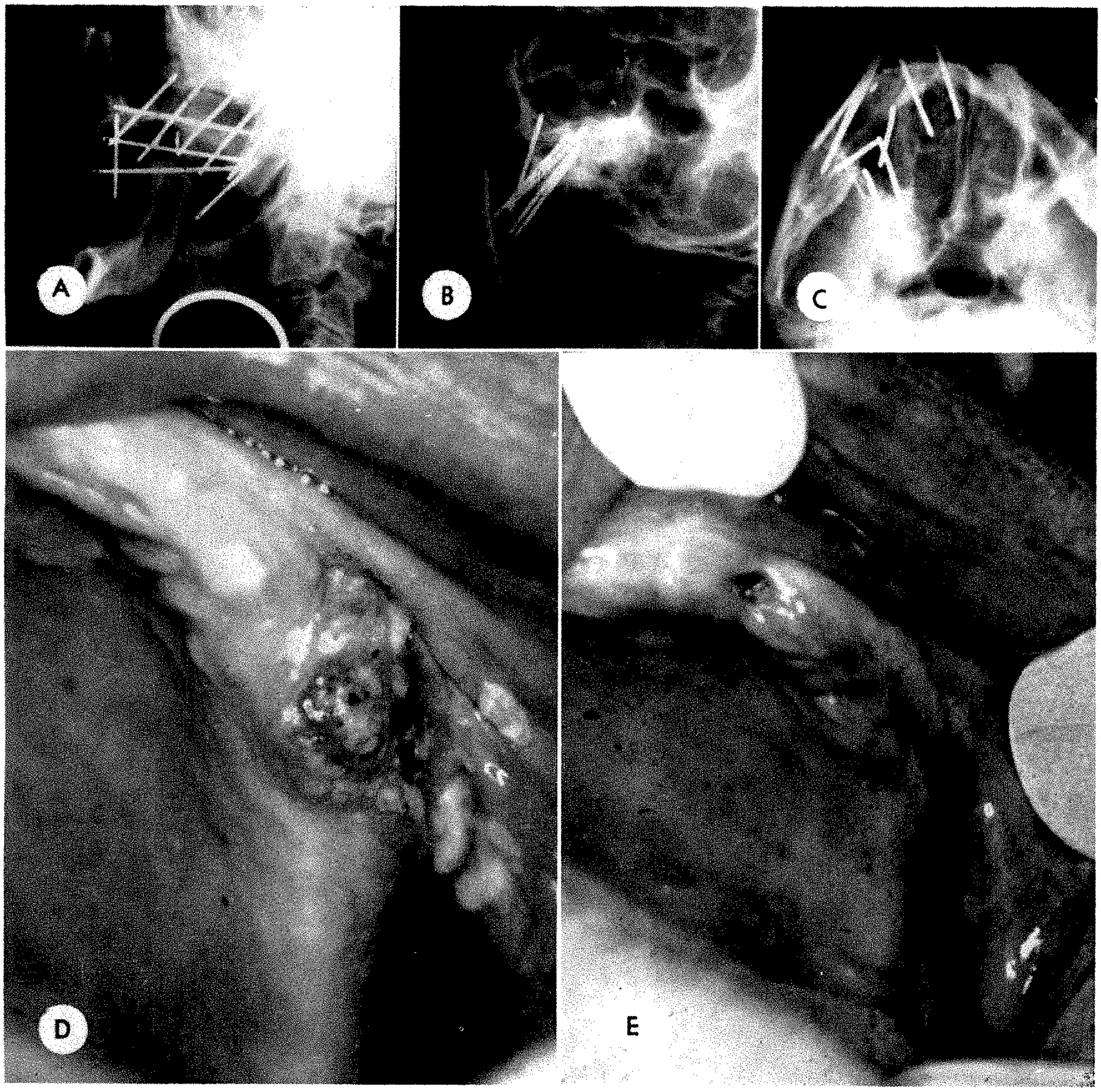

Fig. 27. W.C. 73 W M. *Squamous cell carcinoma of the upper gum with invasion of the adjacent bone and extension to the upper gingivobuccal sulcus and buccal mucosa.* No lymph nodes were palpable. Interstitial radium alone was used.

(*A*, *B* and *C*) An angulated 2-plane pattern implant was applied with the inner plane going through the upper alveolar ridge into the cavity of the maxillary antrum. The outer plane was implanted through the buccal mucosa into the soft tissue of the cheek. A maximum of 7,500 r and a minimum of 6,000 r was estimated as the dose delivered during the 120 hours the implant remained in place.

(*D*) Lesion before treatment. (*E*) The patient developed a brisk, confluent mucositis of the treated area which healed quickly after the treatment. There was good healing of the mucosa and bone. The dimple in the upper gum is one area which is recessed, not perforating, and well epithelized. The patient is free of disease 19 months after treatment.

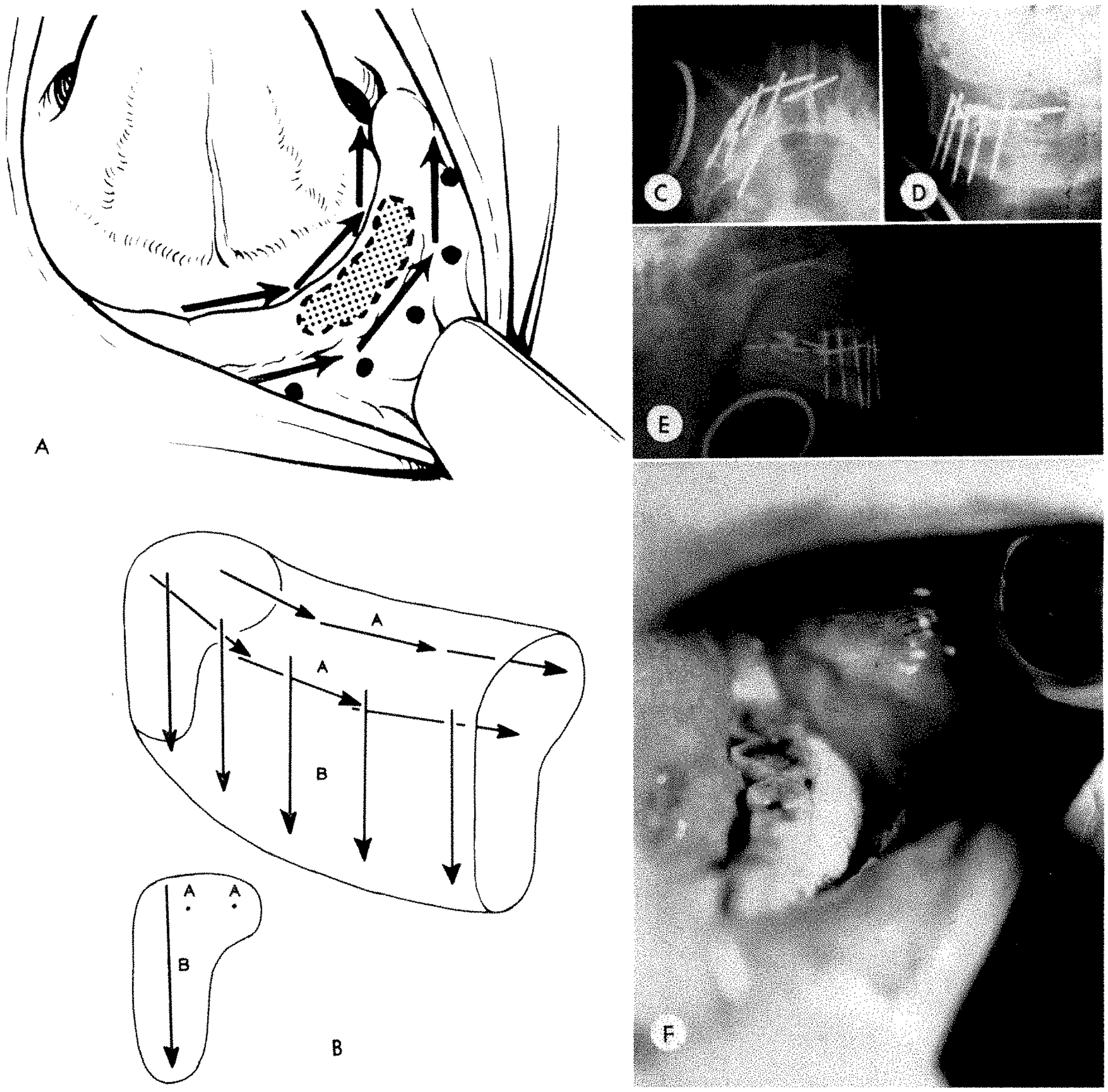

Fig. 28. C.R. 75 W F. *Squamous cell carcinoma of the left gingivobuccal sulcus with invasion of the adjacent lower gum (including bone) and buccal mucosa.* The lesion was on a leukoplakic background. The patient had been a "snuff-dipper" for many years. No lymph nodes were palpable. The teeth were in poor condition and some were loosely imbedded in the tumor; they were removed before treatment. Combined treatment by telecobalt therapy with a single field and interstitial radium was planned.

(*A-E*) The interstitial therapy consisted of a complex pattern composed of 2 right angle plane implants, the vertical plane going through bone and the horizontal plane inserted in the mucosa of the gum covering the whole tumor and the patches of leukoplakia, as shown in the sketches (*A* and *B*). At the time of the implant the residual tumor was represented only by an ulceration in the gum as shown in the sketch (*A*). The dose of the external beam radiation was estimated at the tumor to be 4,500 r delivered in 4 weeks. With the implant a dose of 2,500 r was planned, but the patient pulled the needles out after 1,500 r had been delivered in 48 hours, and refused to have further treatment. The reaction was mild.

(*F*) Lesion before treatment. After 4 months of complete healing recurrence developed in the area. The recurrence was small in the bone with ulceration of the mucosa of the lower gum. The patient refused surgery.

Comment. The treatment was obviously insufficient for a well-differentiated squamous cell carcinoma invading bone which probably would require 7,000 to 8,000 r total dose to be controlled.

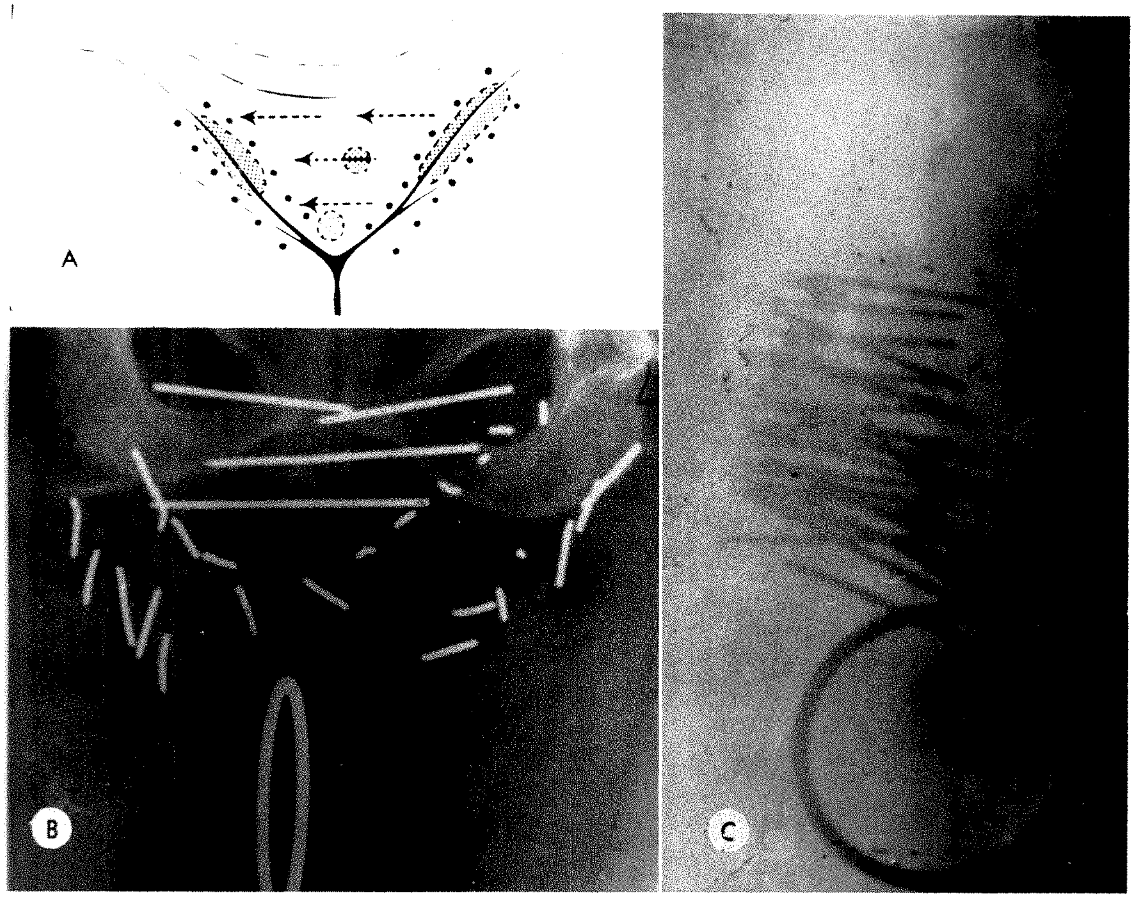

Fig. 29. M.W. 50 N F. *Recurrent cutaneous and subcutaneous tumor after total vulvectomy and bilateral groin dissection.* Combined 220 kv. of roentgen therapy and interstitial radium was indicated.

(*A*, *B* and *C*) An implant of the complex pattern type was used. The folds of the groin were sutured together on each side to ensure that the whole area would be included within the two planes. A single plane was used to irradiate the cutaneous tumors in the mons veneris. A tumor dose of 4,000 r in 5 weeks was given with conventional therapy. An additional 3,000 r in 100 hours (average) was delivered by interstitial radium 2 weeks after the external irradiation was completed.

The treatment was well tolerated. The patient developed a perianal recurrence 1 year later, which was treated by a volume radium implant, and is now free of disease 2 years after the treatment.

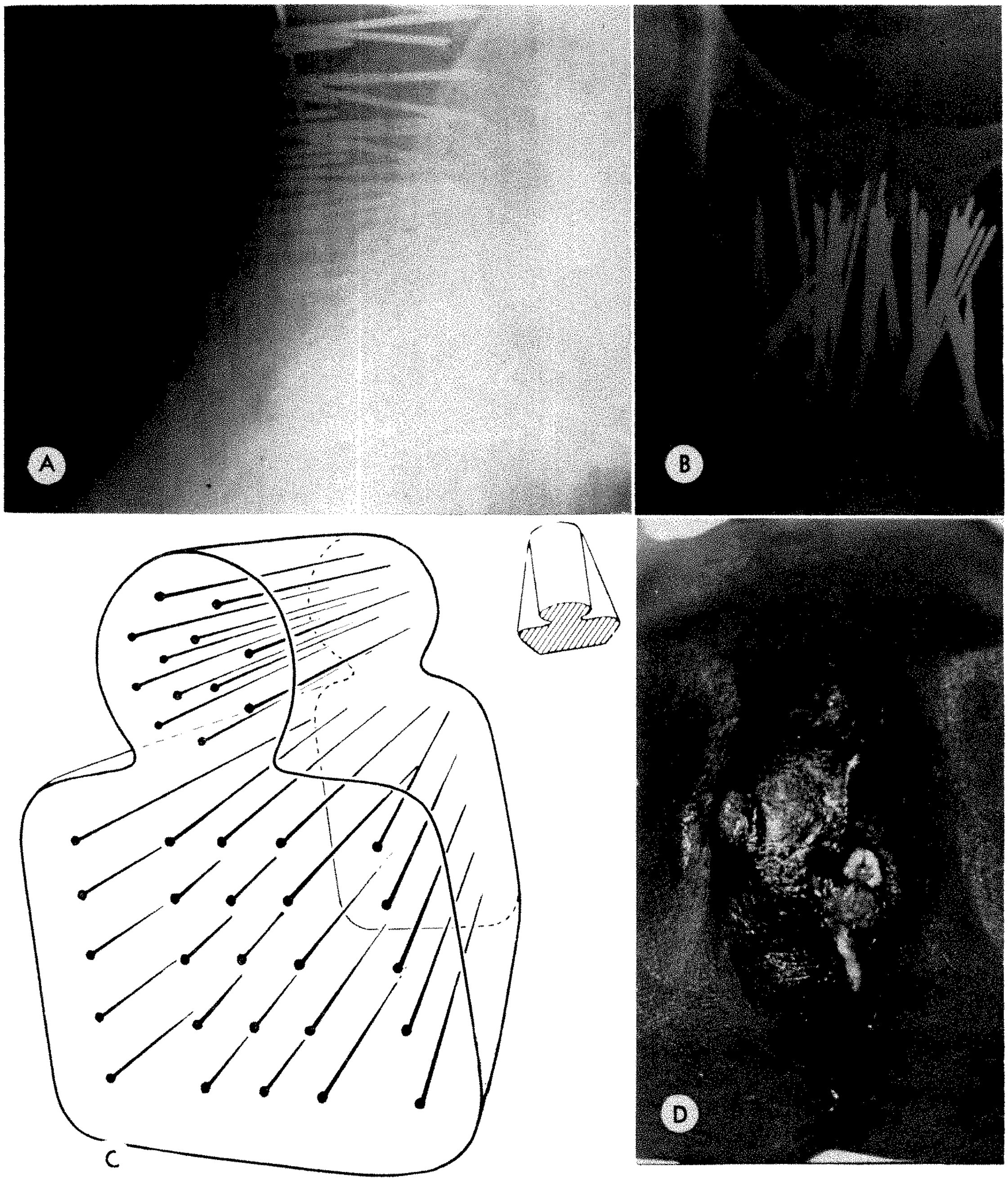

FIG. 30. M.C. 48 N M. *Recurrent squamous cell carcinoma after radical amputation for carcinoma of the penis.* It was decided to use combined 220 kv. roentgen therapy and radium implantation.

(*A*, *B* and *C*) The radium implant was of a double volume pattern. A tumor dose of 3,000 r in 3 weeks was delivered by external irradiation, and 4,000 r in 48 hours by the radium implant.

(*D*) Lesion before treatment. The tolerance was good and the mass disappeared leaving a urethral fistula. When seen 4 months later, the patient had no obvious tumor; he died 6 months after therapy of unknown causes.

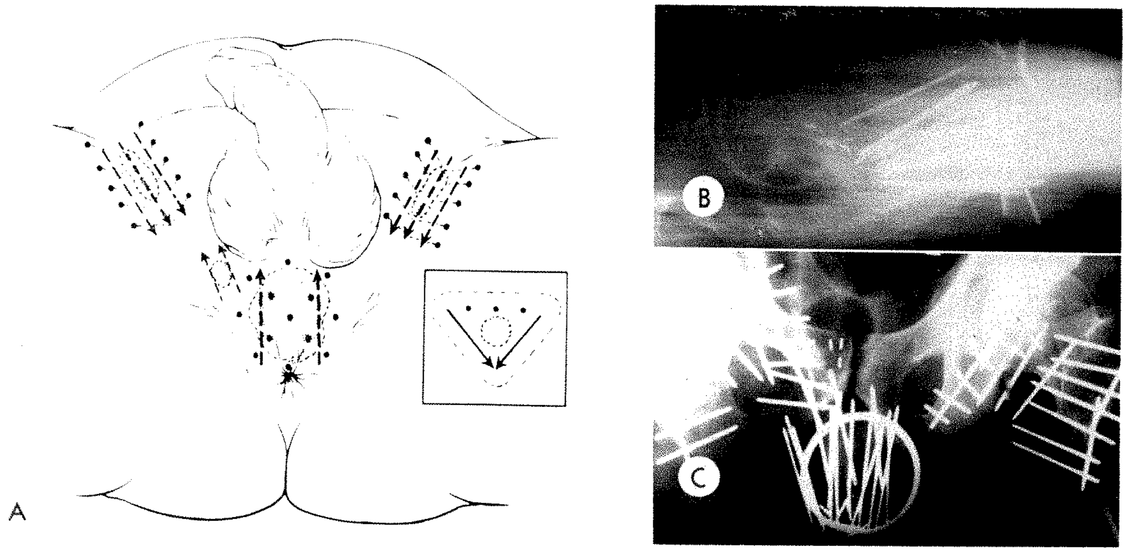

Fig. 31. J.G. 54 W M. *Multiple recurrences of carcinoma of the bladder 4 years after total cystectomy and radon seed implantation in a prostatic extension.*

(*A*) Sketch showing site and extension of the disease and the planned radium pattern. A palliative treatment was indicated because of the slow evolution of the process.

(*B* and *C*) A complex pattern radium implant was used consisting of a volume and small single plane in the perineum, and a 3-plane triangular arrangement for each groin. A dose of 6,000 r was delivered by the volume implant and 5,000 r to each groin by the triangular arrangement in 96 hours.

The treatment was well tolerated and all the lesions disappeared. The patient died 6 months later with distant metastases but with the treated lesions under control.

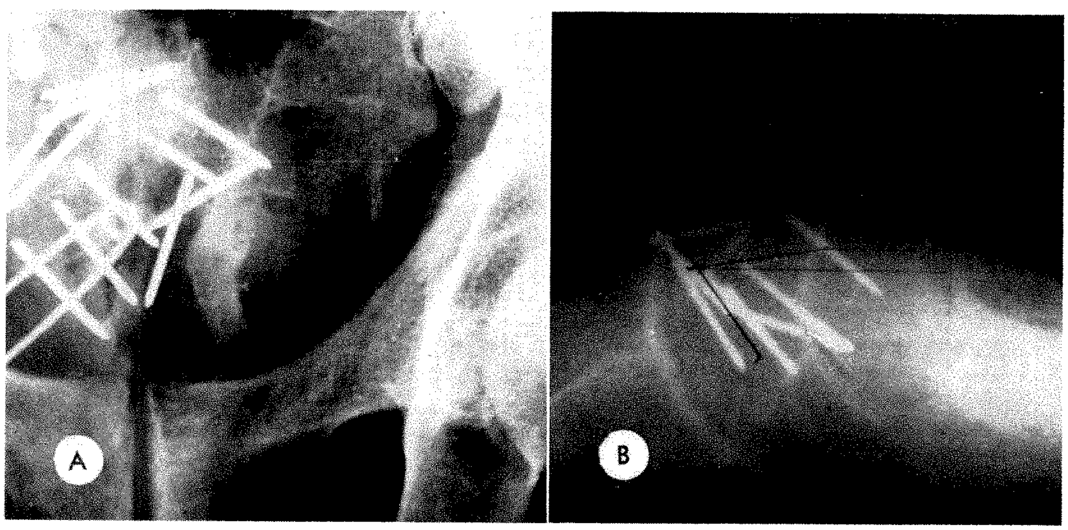

Fig. 32. *Residual carcinoma of the bladder following roentgen therapy.* (*A* and *B*) An interstitial radium implantation was performed through a cystotomy.

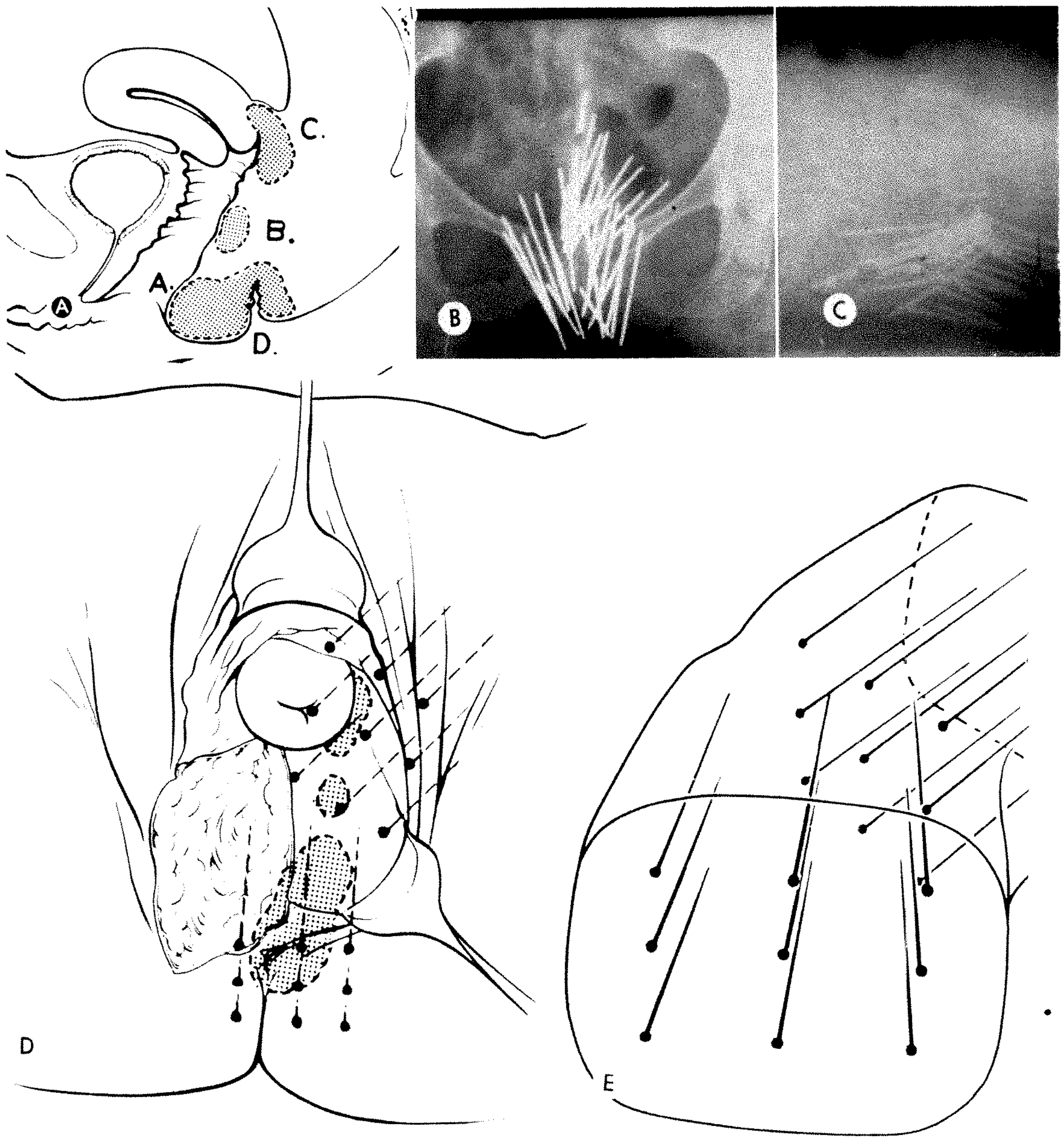

Fig. 33. E.F. 45 W F. *Multiple recurrences from an adenocarcinoma of the rectum, 6 months after a Miles' operation, with resection of the posterior vaginal wall.*

(*A*) Location of recurrences. The vagina was so narrowed as to prevent proper implantation being carried out. It was decided to use interstitial radium therapy alone. A colpotomy was necessary in order to reach the upper masses (*D*).

(*B* and *C*) A complex pattern implantation composed of 2 volumes was performed partially through the "enlarged" vagina and partially through the skin of the perineum. A tandem was inserted in the uterus to increase the dose medially. The volume of irradiation obtained is shown in idealized form in *E*. The dose delivered was estimated to be between 6,000 and 7,000 r in 94 hours.

The patient had a fair reaction with delayed healing of the colpotomy and is presently free of tumor after 16 months.

CONCLUSION

Some of the objections to interstitial gamma therapy are valid ones, but it is also true that if the same enthusiasm and ingenuity that have been devoted to the development of external beam irradiation were applied to this field, interstitial therapy would be more widely employed and the objections against it reduced. The examples cited illustrate that interstitial gamma-ray therapy can be used even where indications are unusual, obtaining good results with a minimum of late changes and without undue complications.

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RADIATION TREATMENT OF CANCER OF THE MOUTH, PHARYNX, LARYNX AND NECK*

A RECORD OF SUCCESSFUL RESULTS

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INTRODUCTION

IT IS the purpose of this paper to present a concise, factual record of successful results obtained by radiation therapy in several forms of head and neck cancer treated at Memorial Hospital during the twenty-four year period from 1931 through 1954. It is furthermore purposed to make a practical analysis of these successful treatment techniques and dosages. There is little value in dwelling on methods which have never succeeded.

Fractionated radiation therapy of head and neck cancer began at Memorial Hospital in 1931. At that time we knew nothing of the dosage factors used by others as such data had not been published. We did know that roentgen therapy given in daily doses over a period of three to six weeks produced an intense reaction in the irradiated tissues, followed by gradual healing and, in some instances at least, by a complete disappearance of the tumor.

In the beginning our treatment was planned mostly by guesswork. As time went on those techniques which succeeded were retained and those which always failed were discarded. By such a process of trial and error, we have arrived at the successful techniques and dosages described in this report.

At no time during this period has our attending staff assumed that the problem of successful radiation therapy has been solved. The techniques have been flexible; there has always been an element of empiricism in arriving at total dosage and the physical factors employed have been somewhat influenced by the available equipment. New ideas and techniques have and are being constantly applied to special cases. With further understanding of the effects of ionizing radiation on cancer and with improved design in physical equipment, changes and modifications in radiation therapy will be in order. In the meantime, a record of successful treatment methods used in the past has been helpful to us in outlining radiation therapy for patients today.

SOURCE OF CLINICAL MATERIAL

A careful search of the Memorial Hospital records and of the office records of our attending staff on the Head and Neck Service was made for the years 1931 through 1954. An over-all period of twenty-four years was studied and only those patients remaining alive and free of cancer for five years or more are included. A positive biopsy was obtained from every cancer case recorded in this report. Additional successful cases have been discovered from time to time which were not found in the original search; these cases have been added.

TYPE OF CLINICAL MATERIAL

As would be expected, the kind of head and neck cancer selected for this study comprises those tumors which were most frequently and successfully treated by radiation. Such cancers were found in the mouth, pharynx, larynx and neck and are listed in the order of their relative frequency in Table I.

Moreover, the cases recorded here are restricted to those in which the successful end result can be unequivocally credited to

* From the Head and Neck Service, Memorial Hospital, New York, New York.
Presented in part at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960.

Table I

HEAD AND NECK SERVICE, MEMORIAL HOSPITAL, NEW YORK CITY

SUCCESSFULLY IRRADIATED CASES

1931–1954 Inclusive		Positive Biopsies from All Tumors
Cancer of the Tongue		
a. Anterior two thirds	119 cases	
b. Base of tongue	55	
Subtotal		174 cases
Cancerous (metastatic) Neck Lymph Nodes		113
Cancer of the Tonsil		101
Cancer of the Nasopharynx		78
Cancer of the Floor of the Mouth		51
Cancer of the Extrinsic Larynx		50
Cancer of the Soft Palate		36
Cancer of the Cheek (buccal mucosa)		30
Total		633 cases

radiation therapy alone. A great many more than an equal number of "cures" was obtained by a combination of radiation therapy and surgery or by surgery alone (see discussion on cancer of the tongue in section on Comment on Successful Cases), but, as the successful results could not be attributed solely to irradiation, these patients were omitted. Approximately 100 successful cases were found in which the radiation therapy used was so arbitrary and variable as to make them unsuitable for group analysis; these patients were not included. Also excluded were those patients whose primary cancers in the head and neck were controlled by radiation but who died in less than five years either of other causes or of distant metastatic cancer.

It must also be pointed out here that several fairly common anatomic forms of mouth cancer are not included in this review. Cancers of the lips, gums, hard palate, paranasal sinuses and salivary glands are considered by us to be best treated by surgery; too few of these patients received their initial treatment by radiation to permit any useful group analysis.

Returning now to the patients comprising this study, most of them were afflicted with squamous or epidermoid carcinoma; there were some lymphosarcomas and a very few adenocarcinomas. In general, the histology and grade of the cancers did not influence the amount of treatment given. Usually, it requires large amounts of radiation to destroy any given cancer, regardless of whether it is epidermoid carcinoma or lymphosarcoma. The surprising fact here was that any adenocarcinomas at all were "cured" as most of them are resistant to irradiation. There comes to mind a thirty-three year old patient suffering from a 5 cm. adenoid cystic type of adenocarcinoma in the base of the tongue. This lesion permanently disappeared following the use of rather heavy roentgen radiation and radon seeds (4,550 r $\times$ 2 through bilateral 7 cm. lateral ports plus 21.8 mc in two doses of seeds) only to have the patient die seven years later of widespread pulmonary and skeletal metastatic cancer.

All of our successful cases fell within the treatment ranges as described in the sections on Radiation Treatment Techniques. It was interesting to observe that as additional "cured" patients were found in the latter part of our search, they also and almost without exception were within the same ranges. Successful cases treated by us since 1954 mostly followed the same pattern.

THE SUCCESSFUL CASES

Table I is as complete as possible and includes all the successful cases found up to the time of writing this report (February, 1960). The order of listing adheres to the relative frequency of the various anatomic forms of cancer. This list of 633 cases represents in all likelihood the largest collection of successful results by "pure" radiation therapy that we will ever assemble on our Head and Neck Service because of our ever increasing reliance on surgery at some point in the treatment of most of these types of cancer.

Table I indicates that cancer of the

tongue was the most common tumor treated. Furthermore, the tongue is divided into its anterior two-thirds and the base, as the treatment techniques for the two areas are different. Also, cancer occurred about twice as often in the anterior part of the tongue.

Most of the 113 patients with metastatic neck lymph nodes also had successfully irradiated cancers elsewhere in the mouth or pharynx. Such patients are listed two or more times, once under each of the respective sites treated. A few patients had two unrelated and successfully treated primary cancers; these patients are also listed twice. Therefore, it can be understood that the total number of cases recorded is actually greater than the number of patients treated. However, in each instance a proved deposit of cancer was treated and controlled.

COMMENT ON THE SUCCESSFUL CASES

One of the more interesting discoveries to come out of the study of the hundreds of hospital records from which these cases were selected was the regularity with which the various types of successful cases fell into the same recognizable treatment "pattern." It is true that many failures also occurred in these same patterns but only very isolated successes were found outside them. Some cancers are just not curable as yet by any known type of treatment.

It is apparent also that many of these 633 successful radiation cases would now be treated by surgery. During the last two years of this study (1953 and 1954), not a single cancer of the anterior two-thirds of the tongue, floor of the mouth, cheek or extrinsic larynx could be found which was successfully treated by radiation alone. Surgery is being used for most mouth cancers, especially when the lesions encroach on either the mandible or maxilla. Our policy of laryngectomy for all resectable cancers of the extrinsic larynx has improved our five year salvage (based on total experience) from 10 per cent to 30 per cent. Interestingly enough, there were 21 instances during these last two years in which radiation controlled metastatic cancer in neck lymph nodes even though neck dissection is now the preferred treatment.

This list of 633 successful cases is a selected collection and is of no value in determining end results. For example, during the fifteen year interval 1939 through 1953 a total of 1,554 cancers of the tongue was seen with a salvage of 467 cases, representing a gross five year cure rate of 30 per cent and a net rate of 35.4 per cent among the determinate patients. Although our list of successful radiation cases covers the longer interval of twenty-four years, there are only 174 patients with cancer of the tongue. These 174 successful cases comprise only a fragment of our total experience and cannot be used alone to calculate a meaningful end result.

In this study we are concerned exclusively with the good results of radiation. When embarking on a course of radiation treatment for a particular patient, it is useful to have at hand a record of past successes as a guide. This supplies us with a pattern of successful performance; we have found it extremely helpful and will continue to use it until something better is available.

RADIATION AGENTS, FACTORS AND DATA

As would be expected over a twenty-four year period in a busy hospital in which radiation therapy is given to a great number of patients, the apparatus was both altered and replaced, so that all our cases were not treated with the same equipment. However, the changes were not radical and the general principles of our treatment program remained essentially the same. At its best, clinical radiation therapy is an inexact and empirical treatment method—one of its frustrating aspects.

ROENTGEN THERAPY

The roentgen therapy machines used in treating the cases in this study are in the high voltage (200–250 kv.) and low voltage (100–130 kv.) category.

High Voltage Roentgen Rays. We em-

ployed high voltage roentgen rays on all cancers which lay at or involved tissues at a depth greater than 2 cm. from the surface of the skin or mucous membrane. At the beginning we used a machine operating at 200 kv., filter 0.5 mm. Cu, half value layer 0.9 mm. Cu, and target skin distance 35–70 cm. Later on, some treatment was given at 220 kv., filter 0.5 mm. Cu, half value layer 1.0 mm. Cu, and target skin distance 35–60 cm. Finally, we used the machine, the one still in use, which operates at 250 kv., filter 1.5 mm. Cu, half value layer 2.0 mm. Cu and target skin distance 35–50 cm. The longer target skin distance was frequently used in treating the more deeply seated tumors although the difference in depth dose at 50 cm. target skin distance compared to 35 cm. target skin distance is probably of little clinical value. For example, through a 4 cm. cone the depth dose at 5 cm. with a target skin distance of 50 cm. per 100 r in air is about 55 r. When the target skin distance is changed to 35 cm., the dose at 5 cm. is 50 r and the treatment time is halved.

One interesting and important clinical observation was made by us during these years. As the potential of our roentgen-ray machines was increased from 200 kv. to 250 kv., the tissue reaction at the treatment site was less intense for the same air dose. It was necessary for us to increase the air dose 15 to 20 per cent to produce the same tissue reaction at 250 kv. which we were accustomed to see with the lower dose at 200 kv.

Low Voltage Roentgen Rays. We preferred low voltage peroral roentgen rays to treat superficially located cancers of the oral mucous membranes. The physical factors of our machine are 100–130 kv., filter none (except the tube wall, a 1.0 mm. Al equiv.) to a 0.1 mm. brass plus 0.25 mm. Al, half value layer 1.2–5.2 mm. Al and target skin distance 15–30 cm. The higher voltage, added filters and longer target skin distance were used for the more deeply infiltrating surface cancers. This machine is very flexible and can be easily adjusted to deliver accurately localized peroral treatment (Fig. 1). The rapid output at 100 kv. with no added filter and at 20 cm. target skin distance (500 r in air in 2.4 minutes) enables a patient to remain perfectly quiet even during a somewhat uncomfortable peroral set-up.

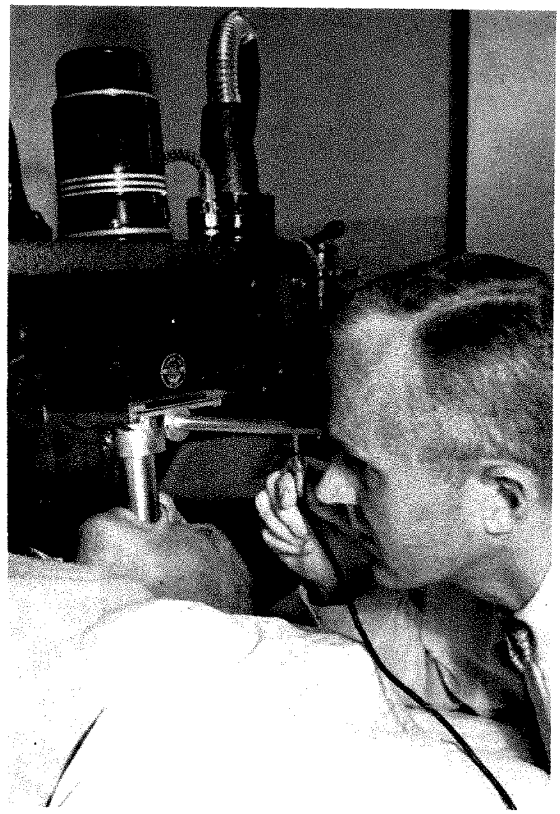
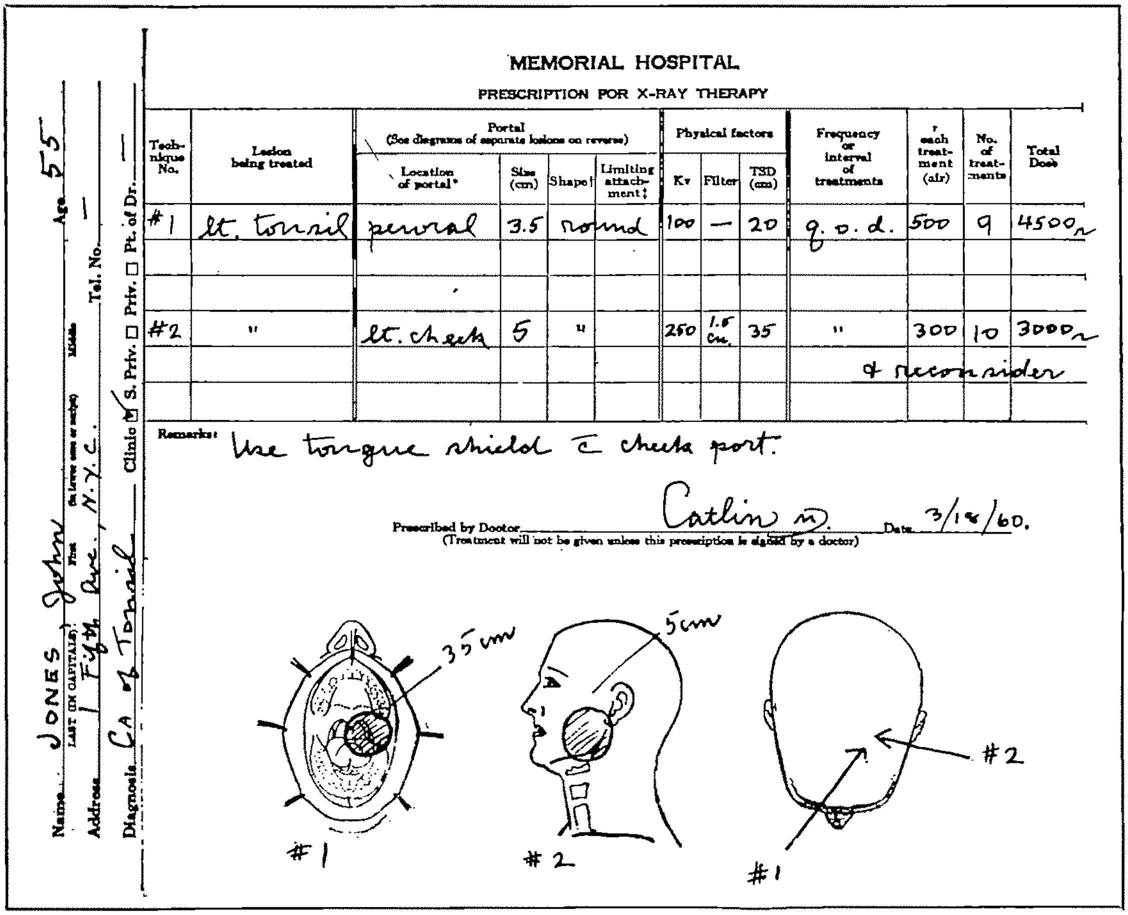


Fig. 1. Low voltage (100 kv.) roentgen therapy. The position of the peroral cylinder is checked by the therapist using an electrically lighted periscope.

Position and Size of Port. In contrast to some of the other physical factors of radiation therapy, the importance of portal position and size should be understood and can be carefully controlled. On our prescription form for radiation treatment, we indicate the ports, using anatomic diagrams to show their exact position and the direction in which the roentgen-ray beam is to be aimed (Fig. 2). Round or oval ports are employed almost exclusively to eliminate useless corners and thereby reduce the total volume of irradiated tissue by a significant amount (Fig. 3). We concentrate our effort on selecting the smallest port that will cover the cancer with a reasonable margin of surrounding normal appearing



MEMORIAL HOSPITAL

PRESCRIPTION FOR X-RAY THERAPY

Name JONES, John — LAST (IN CAPITALS) First Middle — Age 55

Address 1 Fifth Ave., N.Y.C. Tel. No.

Diagnosis CA of Tonsil — Clinic ✓ S. Priv. □ Priv. □ Pt. of Dr.

Technique No.	Lesion being treated	Portal (See diagrams of separate lesions on reverse): Location of portal*	Size (cm)	Shape†	Limiting attachment‡	Physical factors: Kv	Filter	TSD (cm)	Frequency or interval of treatments	r each treatment (air)	No. of treatments	Total Dose
#1	lt. tonsil	peroral	3.5	round		100	—	20	q.o.d.	500	9	4500r
#2	"	lt. cheek	5	"		250	1.5 cu.	35	"	300	10	3000r
									& reconsider			

Remarks: Use tongue shield c̄ cheek port.

Prescribed by Doctor Catlin MD. Date 3/18/60.

(Treatment will not be given unless this prescription is signed by a doctor)

Fig. 2. Roentgen-ray treatment prescription form listing treatment factors. Included also are anatomic diagrams showing the exact position of ports and the direction of the roentgen-ray beam.

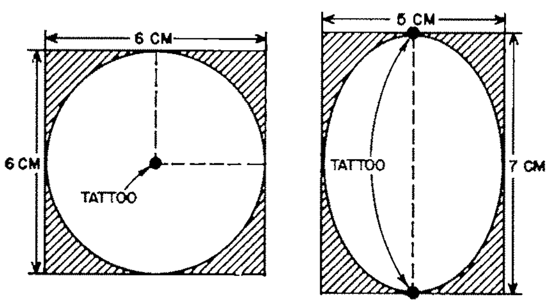


Fig. 3. Diagrams showing round and oval roentgen-ray ports. By eliminating useless corners the volume of tissue irradiated is reduced approximately 20 per cent. The tattoo marks are made in the skin and facilitate accurate placement of the port for each treatment (see text).

tissue. Two or more ports are employed whenever there is the possibility of cross firing the cancer. In this manner the total radiation dose through each port can be made less than if only a single port is used.

The position of the port is localized on the patient's skin by tattooing. A single tiny tattoo mark is used for a circular port. When two straight lines are drawn at a right angle on the skin from a central tattoo, the treatment cylinder can be perfectly centered by bisecting its circumference with both lines. For an oval port, two tattoo marks are made on the skin to correspond to the edges of the long diameter of the treatment area (Fig. 3). The use of these indelible cutaneous marks permits exact reproduction of the physical set-up day after day until the prescribed course of therapy is completed. In peroral roentgen treatment for accessible mouth cancers, the metal cylinder is accurately centered

over the lesion by visual inspection through an illuminated periscope incorporated into the machine (Fig. 1).

We feel strongly that the best way to destroy cancer is to keep the portal size as small as possible and run the total dose of roentgen rays up close to the limit of normal tissue tolerance. The smaller the port used, the larger the total dose of roentgen rays can be. In this entire study there were only 4 instances where cancer was controlled using a port of 10 cm. diameter or larger.

The use of small treatment ports necessitates the positioning of the patient under the roentgen-ray machine with great care and the prohibiting of motion during the treatment interval. Consequently we insist on contact between the machine and the patient. A metal cylinder (either round or oval) of selected diameter is pressed firmly against the skin (Fig. 4). Several small sandbags are used to help immobilize the head and neck.

All patients are examined frequently during treatment. If the radiation reaction does not appear properly localized, the size, position and direction of the treatment cylinder can be promptly corrected. Reliance on a moderate sized, accurately placed port based on a thorough knowledge of anatomy permits the administration of extremely well directed and effective radiation therapy.

Roentgen-Ray Dosage. Although the full importance of both protraction and intensity of roentgen rays is poorly understood, these factors are of practical value in planning a successful radiation dose. The prescription form is filled in carefully and the treatment is outlined to cover a period of three to four weeks (Fig. 2). Radiation treatments are given either daily or every other day, depending on the number of ports being used. Our patients are examined at frequent intervals between treatment "set-ups." The treatment program can be modified, interrupted, prolonged or completed, depending on the degree of tumor regression, the intensity of the radiation reaction and the tolerance of the patient. The daily and total doses of radiation given to each port have been worked out by trial and error plus a good deal of hard experience. The details of treatment and the dosage data are included in the section on Radiation Treatment Techniques further along in this report.

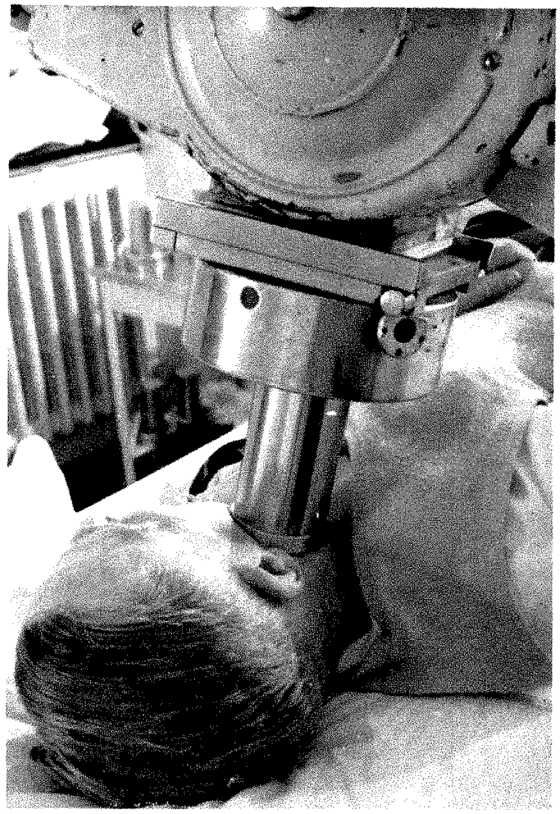


Fig. 4. High voltage (250 kv.) roentgen-ray therapy. Note that the circular cylinder is pressed firmly against the patient's neck to prevent any motion during the treatment period.

The output of our roentgen-ray machines is measured in roentgens delivered in air. Our daily and total doses to each treatment port are expressed also in roentgens in air. The "air" dose is fundamental. It can be easily and accurately measured; it is the basic "applicator" dose from which all other kinds of doses must be derived. Our radiation and physics departments have taken our air doses and from them calculated tissue doses in the various tumors at the center of the roentgen-ray beam. To

complete our treatment record, these central tissue doses are listed adjacent to our air doses in the section under Radiation Treatment Techniques.* Knowing our own inability to determine with any degree of accuracy either the exact position or extent of any given cancer, we place little confidence in the value of a "calculated" tissue dose.

RADON SEED THERAPY

Since 1926 there has been available at Memorial Hospital an apparatus for collecting the radon gas emanating from a solution of radium chloride, the so-called Radium Emanation Plant. Radon gas is pumped into fine gold tubing which is cut and sealed in 4.0 mm. lengths to form our "radon seeds." These seeds vary in radioactive strength from 0.3-3.0 mc. The 0.3 mm. wall thickness of the gold tubing removes by filtration 91 per cent of the beta radiation given off by the radon. The half life of a radon seed is 3.82 days, making it unnecessary to remove it from the tissue into which it is implanted.

Interstitial Radon Implantation. Gold radon seeds are considered by us to be most useful and practical for supplementing roentgen therapy with interstitial radiation. Our practice is to insert seeds whenever possible and not to rely exclusively on roentgen rays to destroy the cancer being treated. We plan to interrupt roentgen treatment about one-half way through the prescribed course and implant the cancer with radon seeds. Following a rest of two to three days roentgen treatment is resumed and, when completed, a second dose of seeds is implanted if any palpable tumor remains. In a few instances even a third dose of seeds may be needed one week later if the cancer has failed to regress completely. In the early years of this study we used seeds containing 1.5–2.0 mc each and frequently implanted a total amount of 30–40 mc.

Further experience taught us that we could avoid or at least minimize tissue necrosis by using seeds of the strength of 1.0 mc or less and by never implanting more than 20–30 mc in any one area of the mouth or neck.

Radon Seed Dosage. The dose of gold seeds is best expressed as the total number of millicuries implanted. This again (as with r in air for roentgen rays) is the basic "applicator" dose from which all other doses must be calculated. The millicurie hour dose is obtained by multiplying the total millicuries implanted by 133 hours. An approximate tissue dose can be calculated by estimating the volume of tissue implanted and assuming that the seeds have been uniformly distributed in the treated area. Such tissue doses have been calculated for the seeds by our Radiation Physics Department and are included in the section on Radiation Treatment Techniques. Clinically, we prefer to rely on the dose of millicuries implanted.

Technique of Radon Seed Implantation. The implantation of gold seeds is not difficult and with care a reasonable, although not perfectly uniform, distribution of sources can be obtained. With a local infiltration of novocain, a trocar is used to carry the seed through a puncture wound in healthy skin into the cancer, thus avoiding direct trauma to an ulcerated and superficially infected tumor. Intravenous pentothal is occasionally used when implanting a tender, painful cancer in the mouth or pharynx. Cancers of the tongue, floor of the mouth, and tonsil lend themselves well to implantation through the skin of the upper neck (see diagram in section on Radiation Technique for Cancer of the Floor of the Mouth). Metastatic neck lymph nodes are implanted directly through the overlying normal skin (see diagram in section on Radiation Technique for Cancerous Neck Lymph Nodes). We try as nearly as possible to implant the seeds 1.0 cm. apart; perfect distribution is impossible, but a good spacing of seeds is facilitated in those cases in which no trocar is removed until the whole implantation is completed. Despite this somewhat crude and empirical method of using interstitial radiation, the

* The author wishes to express his appreciation to Mr. Richard F. Nelson and Dr. John Laughlin of the Physics Department for the dosimetry analysis of the external radiation and of the interstitial radon applicators.

clinical effect is often most gratifying; it has aided on many occasions in the permanent destruction of deposits of cancer.

Nasopharyngeal Radon Seed Applicator. In treating cancers of the nasopharynx, the use of interstitial radiation is impractical because most of these tumors are too small to be implanted with radon seeds. Consequently, we use a small brass applicator (filtration: 2.2 mm. brass equiv.) containing radon seeds which is inserted through the nasal cavity so as to rest adjacent to the cancer (see diagram in section on Radiation Technique for Cancer of the Nasopharynx). The brass capsule on the applicator is loaded with 12–14 mc of radon sufficient to give a dose of 500–600 mc hr. in forty-eight hours. In this type of intracavitary radiation, the dose must be expressed in millicurie hours and not in millicuries implanted as the applicator is removed after a specified interval. It is our practice to insert the nasopharyngeal applicator one-half way through the course of roentgen-ray treatment.

A technique of radiation therapy using a combination of roentgen rays and radon seeds makes it possible to keep our treatments within the range of previous successes without being forced to use the maximum amount of either agent. Such a program seems to us both reasonable and practical.

RADIATION TREATMENT TECHNIQUES

• In this section nine different techniques are given for treating nine different anatomic forms of mouth, pharynx, larynx, and neck cancer. Not all of the successful cases included in this report were treated only by the nine techniques described. Some of the earlier cases were treated with different roentgen-ray machines and with some modifications in the other treatment factors.*

Despite frequent minor variations, the basic principles of our treatment have remained the same. The techniques described here are the ones in current use on our Head and Neck Service and seem to be the most satisfactory to date. No originality or infallibility is claimed for these techniques; they are simply the treatment methods which have been most often successful in our hands.

In describing these treatments the adjectives "median" and "range" are purposely used to modify the size of the lesions and roentgen-ray ports, all the doses, and the length of therapy. The *median figure* is one around which the greatest number of successes was found. The *range figures* denote the limits in variation in size and other factors within which all our successful cases lay. The median figure coupled with its range of successful values is more accurate and informative than a single average figure. Almost no controlled cases were found outside the ranges listed; those which were, are too bizarre for useful analysis. Attention is directed to the very broad range in doses in most of our techniques. This is best explained by the marked variation with which supposedly similar cancers respond to identical forms of radiation treatment. One cancer will completely regress with a dose of "X" roentgens; a second, similar appearing cancer will show only a moderate degree of regression following a dose of "2 X" roentgens, and so forth. Little is yet understood about this biologic difference in cancers.

In general, it can be stated that, in most instances where the portal size is small, the total dose of roentgen rays will lie at the high end of the range. Conversely, when the port is large, the roentgen-ray dose tends to be at the low end of the range. Also the total dose of roentgen rays is usually influenced by the amount of interstitial radon seeds used; the greater the number of seeds implanted, the nearer the lower end of the range is the total dose of roentgen rays and vice versa. The same can be said for the individual doses of roentgen rays, which also tend to vary inversely with different portal sizes; the lower doses are coupled with the larger ports and vice

* Those readers interested in examining our other treatment techniques are referred to the manual "Treatment Factors in Radiation Therapy of Cancer of the Mouth, Pharynx and Larynx" by Hayes Martin, M.D. Published by United Surgical Supplies Co., Mamaroneck, New York, 1954.

versa. The length of the treatment period is largely governed by the number of ports used and individual set-ups needed to complete the outlined course. Those cases which require multiple ports are under treatment the longest (for more about protraction of treatment see Discussion section).

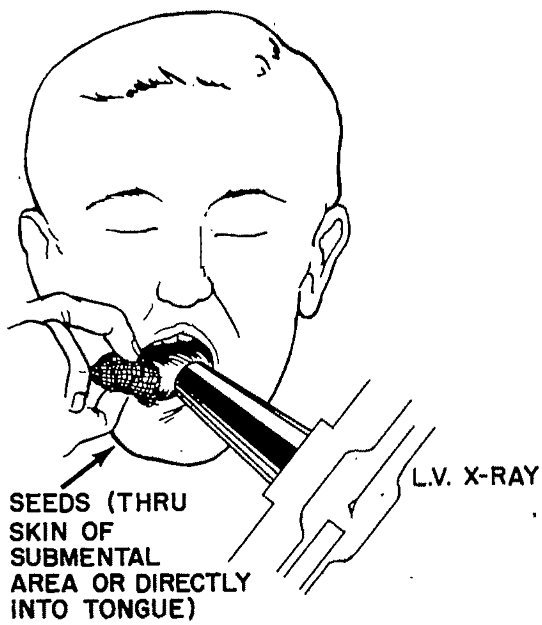
All the above mentioned facts become increasingly self evident with practice. The important thing to remember in treating new cases is to approximate these *mean* doses when feasible and always be doubly certain that the program of treatment is so planned as to lie within the *range* of previous success.

In the following descriptions of radiation techniques all roentgen-ray doses are expressed in "roentgens in air," except when specified otherwise.

RADIATION TECHNIQUE FOR CANCER OF THE ANTERIOR TWO-THIRDS OF THE TONGUE

Comment. In this group of 119 successfully treated patients, the largest number (61) were treated by the combination of low voltage peroral roentgen therapy supplemented with gold radon seeds. We favor the low voltage apparatus for peroral set-ups because of its extreme flexibility and the accuracy with which the treatment cylinder can be centered on the cancer. Radon seeds are implanted either directly into the tongue cancer or preferably through the skin of the submental area when possible; they augment the depth dose around and within the cancer. In most of these patients the radon seeds were implanted in a single dose or in two doses divided by a seven to ten day interval during the course of peroral roentgen irradiation. The larger doses of radon were given in association with the lower total doses of roentgen rays. In 9 patients no radon seeds were used at all because of rapid and complete regression of their tumors with roentgen rays alone. One 8 cm. tumor was actually 8×3.5 cm. and the largest practical cylinder (4 cm.) was used tangentially, thereby covering the whole diameter of the cancer. In recent years we have preferred surgery for cancers located in the anterior two-thirds of the tongue.

Low Voltage Roentgen Rays.
One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
Gold Radon Seeds.



Size of Tongue Cancer.
Median diameter 2 cm. (range 1–8 cm.)
Roentgen Therapy.
Peroral Port: Median diameter 3 cm. (range 2–5 cm.)
Individual Dose: Median 600 r (range 350–1,000 r)
Total Dose: Median 10,000 r (range 3,000–12,000 r) (tumor dose: 6,600 r)
Radon Seeds.
Total Dose: Median 9 mc (range 4–25 mc) (tumor dose: 10,000 r)
Treatment Period.
Duration: Median 30 days (range 12–58 days)

RADIATION TECHNIQUE FOR CANCER OF THE BASE OF THE TONGUE

Comment. Thirty-two of these 55 patients were treated with two lateral ports only, the third suprahyoid port being omitted. The median total dose of roentgen rays and the successful range doses using two lateral ports are: total dose: median 3,800 r×2 (range 2,100 r×2–6,600 r×2). In our more recent cases we have added the third port, our purpose being to reduce

High Voltage Roentgen Rays.
Two lateral ports, one suprahyoid port. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
Gold Radon Seeds.

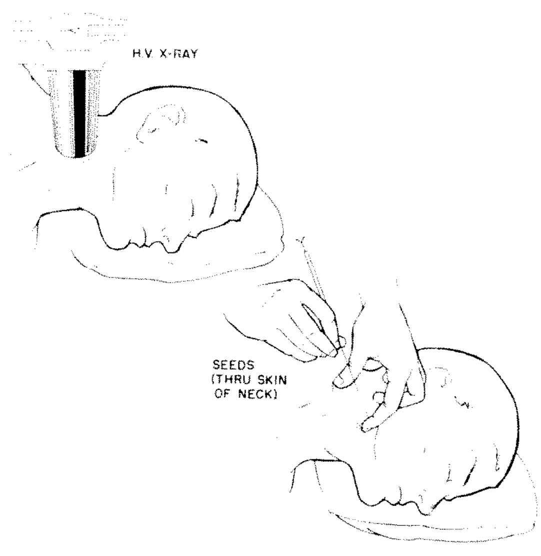
Size of Tongue Cancer.
Median diameter 3 cm. (range 1–7 cm.)
Roentgen Therapy.
Lateral Ports: Median diameter 6 cm. (range 6–7 cm.)
Suprahyoid Port: Median diameter 5 cm. (range 5–7 cm.)
Individual Dose: Median 400 r (range 250–400 r)
Total Dose: Median 3,500 r × 3 (range 3,000 r × 3–4,200 r × 3) (tumor dose: 5,000 r)
Radon Seeds.
Total Dose: Median 23 mc (range 6–35 mc) (tumor dose: 8,000 r)
Treatment Period.
Duration: Median 36 days (range 24–64 days)

slightly the total roentgen-ray dose through each port while maintaining the same or an increased dose to the base of the tongue. The largest base of tongue cancer controlled by radiation was 7 cm. in diameter and was an isolated instance. Large cancers in this area are now attacked surgically, particularly if a metastatic neck lymph node (or nodes) is present on the first examination.

RADIATION TECHNIQUE FOR CANCEROUS (METASTATIC) NECK LYMPH NODES

Comment. During the first ten years or so of this report, the treatment of cervical metastatic cancer was almost exclusively by some form of roentgen therapy. In most instances we employed a single high voltage neck port supplemented with interstitial seeds as outlined in the preceding paragraph. The seeds were usually implanted one-half way through the treatment program with a possibility of a second implantation at the completion of roentgen irradiation if residual cancer was palpable. In a few patients even a third implantation was done. Our tendency was to match the smaller dose of roentgen rays with the larger dose of radon and vice versa. In 10 patients in this group of 113 cases, no radon seeds were used as regression was complete without them. We learned that the single most important factor in controlling neck cancer by radiation was the size of the growth. The smaller the area of metastasis, the better the prognosis. Roentgen-ray ports larger than 8 cm. in diameter were only rarely successful. Larger ports of 10, 11, and 14 cm. were each successful in 1 patient only; a 12 cm. port controlled neck cancer in 2 instances. This serious limitation of effective irradiation to the neck has convinced us that complete neck dissection is the treatment of choice in most of the resectable cases.

High Voltage Roentgen Rays.
One neck port. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
Gold Radon Seeds.

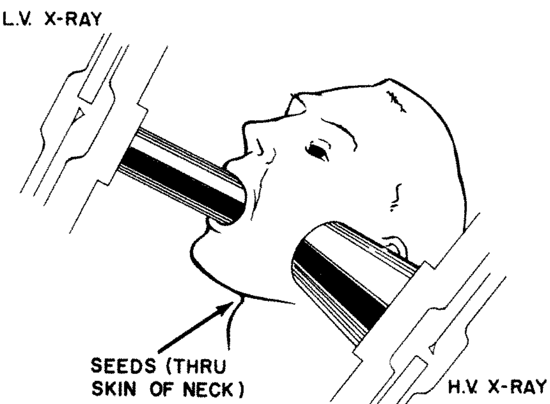


Size of Neck Cancer.
Median diameter 3 cm. (range 1–9 cm.)
Roentgen Therapy.
Neck Port: Median diameter 4 cm. (range 2.5–14 cm.)
Individual Dose: Median 400 r (range 150–1,000 r)
Total Dose: Median 5,000 r (range 3,000–10,000 r) (tumor dose: 3,650 r)
Radon Seeds.
Total Dose: Median 17 mc (range 3.5–27 mc) (tumor dose: 15,000 r)
Treatment Period.
Duration: Median 27 days (range 12–53 days)

RADIATION TECHNIQUE FOR CANCER OF THE TONSIL

Comment. Cancers of the tonsil are frequently undifferentiated and anaplastic. In addition, the tonsil is the most common site in the mouth and pharynx for lymphosarcoma. Consequently, many tonsil cancers are sensitive to and regress quickly under treatment with radiation. Such was our experience with this group but prompt regression of the tumor did not necessarily deter us from delivering a full "cancer-lethal" dose of roentgen rays (even in the lymphosarcomas), usually supplemented with radon seeds. Our early cases were treated with two opposing mandibular ports and we still use this technique in patients in whom peroral therapy is not practical. The roentgen-ray doses for the two high voltage mandibular ports are as follows: total dose: median 4,100 r×2 (range 2,200 r×2–4,500 r×2). During the last few years we have been performing radical operations on many patients with tonsil cancers who also present homolateral metastatic lymph nodes on the first examination.

High Voltage Roentgen Rays.
(A) One mandibular port. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
Low Voltage Roentgen Rays.
(B) One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
Gold Radon Seeds.

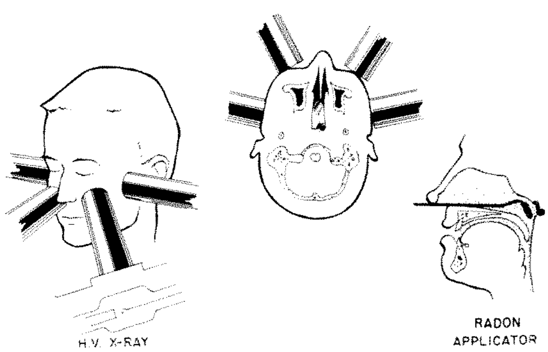


Size of Tonsil Cancer.
Median diameter 3 cm. (range 1–6 cm.)
Roentgen Therapy.
(A) *Mandibular Port:* Median diameter 5 cm. (range 4–7 cm.)
Individual Dose: Median 350 r (range 300–600 r)
Total Dose: Median 4,000 r (range 3,000–6,300 r) (tumor dose: 2,280 r)
(B) *Peroral Port:* Median diameter 3.5 cm. (range 2.5–4.5 cm.)
Individual Dose: Median 500 r (range 400–1,000 r)
Total Dose: Median 7,000 r (range 2,500–9,000 r) (tumor dose: 4,760 r)
Radon Seeds.
Total Dose: Median 9 mc (range 3–25 mc) (tumor dose: 10,000 r)
Treatment Period.
Duration: Median 28 days (range 17–50 days)

RADIATION TECHNIQUE FOR CANCER OF THE NASOPHARYNX

Comment. Although cancers of the nasopharynx are usually small (the largest in our group was 3 cm.), their deep location and intimate contact with the base of the skull will undoubtedly preclude their successful removal by surgery. All our cases were treated by radiation and in the beginning we used only two cheek ports. Somewhat later we added the nasopharyngeal radon applicator and then a third high voltage peroral port. A high incidence of radionecrosis of the soft palate discouraged

High Voltage Roentgen Rays.
Two malar ports; two zygomatic ports. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
Intracavitary Radon Applicator.



Size of Nasopharynx Cancer.
Median diameter 2 cm. (range 0.5–3 cm.)
Roentgen Therapy.
Malar and Zygomatic Ports: Median diameter 5 cm. (range 4–6 cm.)
Individual Dose: Median 400 r (range 200–600 r)
Total Dose: Median 3,500 r × 4 (range 2,100 r × 4–4,100 r × 4) (tumor dose: 5,500 r)
Radon Applicator.
Total Dose: Median 600 mc hr. (range 500–1,600 mc hr.) (tumor dose: 15,000 r)
Treatment Period.
Duration: Median 36 days (range 20–58 days)

continued use of a peroral cylinder. Finally we adopted the technique of four cheek ports supplemented with the radon capsule which remains our treatment of choice now. We cross fire the nasopharynx with multiple ports and avoid giving an excessive dose of roentgen rays through any single port.

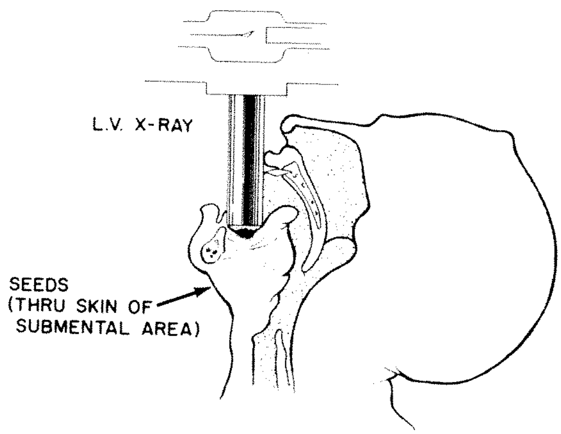
It is customary to insert the radon applicator into the nasopharynx at a stage halfway through the treatment period, at which time the roentgen irradiation is interrupted for four to five days. The applicator remains in the nasopharynx for forty-eight hours. Our early doses of radon were large (approximately 1,000–1,200 mc hr. and in 1 patient 1,600 mc hr.) and, though successful, were frequently followed by persistent radionecrosis and exposed bone. We have learned that the most satisfactory dose for intracavitary radon is 500–700 mc hr.

Most of our patients with nasopharynx cancer also have metastasis to the neck lymph nodes, frequently bilaterally. The nasopharynx cancer is usually destroyed by our irradiation but failure to cure is due to uncontrolled regional or systemic metastasis.

RADIATION TECHNIQUE FOR CANCER OF THE FLOOR OF THE MOUTH

Comment. Radiation treatment of cancer of the floor of the mouth has been most successful in small and centrally located tumors when the adjacent alveolar ridge and mandible could be adequately protected from the destructive effect of cancer-lethal irradiation. In this present series of 51 cases, the largest successfully treated cancer was 6 cm. in diameter; in this case an additional 4,500 r of roentgen rays (200 kv.) was given through a 7 cm. submental port. For most of our patients, we favored the use of a single low voltage peroral port supplemented with radon seeds. The set-up was sometimes difficult and required extraction of some anterior teeth to permit accurate angulation of the peroral cone. Both circular and oval ports were used, care being taken to protect the adjacent alveolar ridge. For this purpose special lead shields were made by our dental department to accurately fit over the lower gum. Radon seeds were implanted through the skin of the submental area with a guiding finger placed on the cancer in the floor of the mouth. Irradiation of more extensive cancers resulted in so much prolonged radionecrosis of the mandible that surgery is now preferred for these larger tumors.

Low Voltage Roentgen Rays.
One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
Gold Radon Seeds.

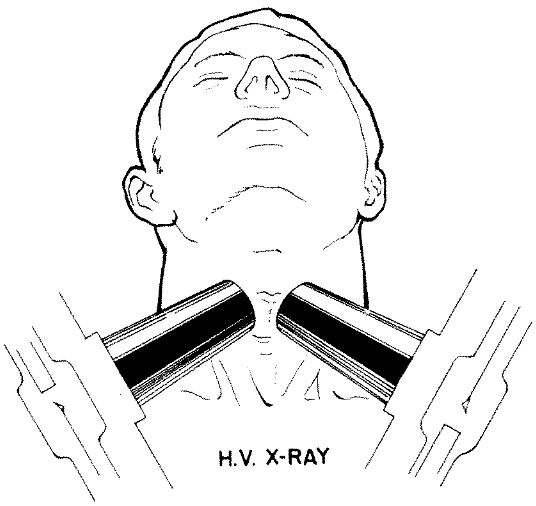


Size of Floor of Mouth Cancer.
Median diameter 2 cm. (range 1–6 cm.)
Roentgen Therapy.
Peroral Port: Median diameter 3 cm. (range 2–5 cm.)
Individual Dose: Median 500 r (range 400–1,000 r)
Total Dose: Median 9,500 r (range 6,000–12,000 r) (tumor dose: 6,270 r)
Radon Seeds.
Total Dose: Median 8 mc (range 5–22 mc) (tumor dose: 9,000 r)
Treatment Period.
Duration: Median 25 days (range 18–35 days)

RADIATION TECHNIQUE FOR CANCER OF THE EXTRINSIC LARYNX

Comment. From 1931 until about 1944 all our patients with extrinsic larynx cancer were treated with some form of radiation. In some of the early cases we tried supplementing roentgen rays with radon seeds, which we either implanted into or placed on the surface of the cancer with an applicator. Following the use of radon seeds, there were frequent complications due to

High Voltage Roentgen Rays.
Two oblique ports. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 50 cm. TSD.



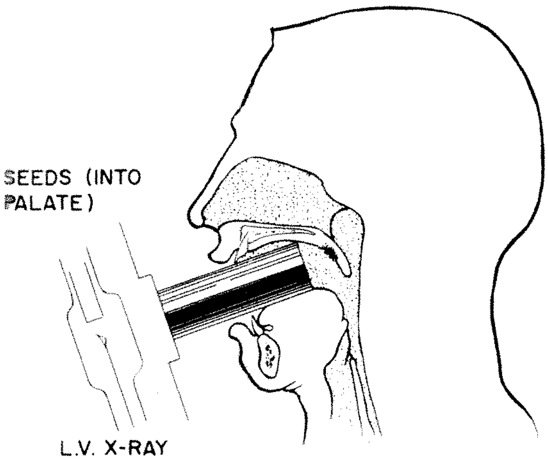
Size of Extrinsic Larynx Cancer.
Median diameter 2.5 cm. (range 1–4 cm.)
Roentgen Therapy.
Oblique Ports: Median diameter 7 cm. (range 5–10 cm.)
Individual Dose: Median 350 r (range 150–500 r)
Total Dose: Median 4,000 r × 2 (range 3,500 r × 2–5,100 r × 2) (tumor dose: 6,000 r)
Treatment Period.
Duration: Median 31 days (range 13–52 days)

slough and necrosis occurring in the larynx. There were very few successes and the radon seeds were soon abandoned. There remains only 1 five year control in which supplementary radon seeds were used in the extrinsic larynx. Radionecrosis in the larynx was a serious complication, usually resulting in failure; there were only 2 such patients in a total of 50 successful cases. As a matter of some interest a careful study was made of 100 cases of extrinsic larynx cancer in which roentgen therapy failed to cure. Larynx cancer was chosen purposely because the roentgen treatment is simple and direct; no radon seeds were used. Only those cases were selected in which the prescribed course of treatment was completed as outlined. Failure was due either to persistent cancer in the larynx or to the lethal effects of radiation such as radionecrosis, hemorrhage and sepsis. Patients with advanced larynx cancer and those who did not complete treatment were excluded from this study. Among the failures, the primary tumors were similar in size and extent to those seen in the 50 successfully irradiated cases. The treatment factors, the median dose, and dosage range were similar for both groups. Successes and failures fell into the same general treatment pattern. In about one-half of the failures, radionecrosis and persistent cancer were coexistent on the same site; a roentgen ray dose sufficient to kill normal tissue was inadequate to destroy cancer. The only reasonable explanation for the difference between success and failure is to assume that some cancers are curable by roentgen rays and others simply are not, regardless of the dose and physical factors used. We finally came to rely entirely on high voltage roentgen rays (200–250 kv.) delivered through oblique circular ports, so directed as to cross fire the larynx. Today we use radiation only for nonresectable cases and for recurrence following surgery. Our preference for surgery as the initial form of treatment in all resectable extrinsic larynx cancers has greatly increased our over-all five year cure rate.

RADIATION TECHNIQUE FOR CANCER OF THE SOFT PALATE

Comment. In this anatomic form of mouth cancer, we used at least 5 different radiation techniques, all of which were, on occasion, successful. Various combinations of external high voltage ports with or without a peroral low voltage port were all used, often supplemented with radon seeds. However, the technique which was most often successful and the one in greatest use now employs a single peroral roentgen-ray port supplemented with implantation of radon seeds. In 2 patients the soft palate cancers were 6 cm. in diameter and were too large to be covered by a peroral cylinder alone. Therefore, two lateral 7 cm. circular, high voltage cheek ports were added for a roentgen-ray dose of 3,000 r×2. A single small cancer of the soft palate was treated successfully with 10.1 mc of radon seeds alone. In most cases the seeds were implanted directly into the tumor through the

Low Voltage Roentgen Rays.
One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
Gold Radon Seeds.



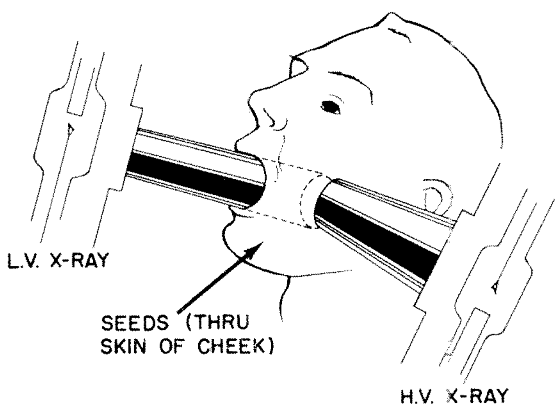
Size of Soft Palate Cancer.
Median diameter 2 cm. (range 1.5–6 cm.)
Roentgen Therapy.
Peroral Port: Median diameter 3 cm. (range 2.5–5 cm.)
Individual Dose: Median 500 r (range 400–800 r)
Total Dose: Median 8,500 r (range 6,000–11,000 r) (tumor dose: 5,600 r)
Radon Seeds.
Total dose: Median 6 mc (range 4–9 mc) (tumor dose: 8,000 r)
Treatment Period.
Duration: Median 25 days (range 16–31 days)

open mouth, usually at the halfway point in the roentgen treatment program. In 2 patients regression of the cancer was complete with roentgen rays and no radon seeds were used.

RADIATION TECHNIQUE FOR CANCER OF THE CHEEK (BUCCAL MUCOSA)

Comment. Here again, roentgen irradiation proved successful mostly in small cancers which were located at a slight distance away from the maxilla and mandible. A single exception was a patient with a large (12 cm.) lymphosarcoma of the cheek which was successfully controlled with roentgen rays alone using a 12 cm. circular high voltage external port for a dose of 3,100 r. In the beginning, a single cheek port was used and the roentgen rays were supplemented with radon seeds. Later on, we added the second peroral port which is the preferred technique now. Radon seeds were used in a little more than one-half of our successful cases. Larger doses of radon were employed with the lower doses of roentgen rays. Implantation of the seeds was made through the skin of the cheek with a palpating finger placed on the underlying cancer. During treatment with the external cheek port, a lead shield was always placed in the mouth to protect the tongue from the roentgen rays. In our experience, irradiation of large cancers of the cheek has resulted in such a high incidence of painful osteoradionecrosis coupled with troublesome trismus that surgery is now preferred in almost all cases.

High Voltage Roentgen Rays.
(A) One cheek port. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
Low Voltage Roentgen Rays.
(B) One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
Gold Radon Seeds.



Size of Cheek Cancer.
Median diameter 3 cm. (range 1–12 cm.)
Roentgen Therapy.
(A) *Cheek Port:* Median diameter 6 cm. (range 2.5–12 cm.)
Individual Dose: Median 400 r (range 250–600 r)
Total Dose: Median 5,100 r (range 3,100–6,500 r) (tumor dose: 3,570 r)
(B) *Peroral Port:* Median diameter 3.5 cm. (range 2.5–4 cm.)
Individual Dose: Median 500 r (range 350–1,000 r)
Total Dose: Median 7,200 r (range 3,600–12,000 r) (tumor dose: 4,900 r)
Radon Seeds.
Total Dose: Median 7.5 mc (range 2–21 mc) (tumor dose: 8,500 r)
Treatment Period.
Duration: Median 25 days (range 15–64 days)

DISCUSSION

Added to the careful study made of many hundreds of hospital records to collect this series of more than 600 successful irradiation cases are twenty years of personal experience in radiation treatment of patients with head and neck cancers. Over the same years there have been regularly scheduled conferences and numerous discussions concerning the management and many problems of radiation therapy among all the attending surgeons on our Head and Neck Service. From such an experience it would seem only natural to form certain impressions and observations on the whole subject. Although not strictly as factual as the reporting of our successful cases, the following comments are based directly on clinical experience and are not just intellectual whimsey.

THE RADIATION REACTION

From the beginning of radiation therapy, clinical observation has revealed that it is necessary to produce an intense reaction in the treated tissues; the reaction must be sufficiently violent and prolonged to destroy the cancer while sparing the normal surrounding tissue. The process is somewhat similar to boiling an egg in water which is heated to 220° F. and held at that temperature for a selected time to cook the egg. To obtain the desired change in the egg it must be kept in the boiling water for a specified interval. The cooking period cannot be altered, interrupted or repeated later and still produce the same change in the egg. Similarly, in giving radiation therapy the tissues must be "heated up" (by ionization) and the reaction maintained until the desired effect (destruction) on the cancer is obtained. This concept helps in understanding why small doses of radiation with minimal tissue reaction are rarely successful and why a "course of irradiation" cannot usually be repeated with a successful outcome at a later date. Like egg boiling, irradiation of a cancer is a single planned operation and any modification of the dose must be made while the reaction is "hot." Unlike egg boiling, where the degree and effect of cooking are known, the exact amount of "heat" required to kill a cancer is unknown. Experience has indicated that we will most often succeed if we deliver the largest dose the normal tissues can tolerate and such has been our practice in most of our cases.

FRACTIONATION (OR PROTRACTION) OF ROENTGEN-RAY TREATMENT

Ever since the first therapists discovered that tissue recovers at a fairly regular rate from the effect of radiation, the massive single dose technique of treatment was replaced by the multiple divided dose method. It was thought that not only could the total dose of roentgen rays be greatly increased by such protracted treatment, but also that the cancer cells could be exposed to ionization at a moment when they were extremely vulnerable (*i.e.*, during mitosis). On the basis of such conjecture, innumerable types of fractionation of the roentgen rays were tried and all sorts of advantages claimed. Despite this past furor of activity, the exact scientific value of protracted treatment remains obscure. Unfortunately, the differential in susceptibility to roentgen rays between cancer and normal tissue is not appreciably broadened by fractionating the total dose. Cancers, like normal tissue, also have a recovery rate.

However, there is a very practical reason (and probably the only good one) for fractionating roentgen treatment. If the exact dose needed to kill a cancer were known in advance, such a dose could be given at a single treatment without further ado. Alas, such a magic dose is never known with certainty at the start of treatment, so that we must fractionate our doses and "sneak up" on the final figure. Protraction gives us the chance to observe the response of the cancer to roentgen rays and to reserve decision as to the total dose until well along in the treatment program. A few more doses can be added to give the "coup de grâce" to the cancer or

the program may be cut short if the reaction warrants it. It is around the "end point" of treatment that the total dose range of our successful experience is so valuable. In brief, protraction of treatment is solely an empirical and practical aspect of roentgen therapy. It is employed to help the therapist arrive at an effective total dose and not for any mystically beneficial effect that it might have on either the cancer or the patient.

Due to the delay with which roentgen rays attain their full effect on tissue, about three to four weeks has proved to be a practical treatment period. The interval is longer when the treatment is complicated by the use of several ports or when there is a delay due to the implantation of radon seeds. Such planning has guided us in our performance on the successful cases reported here.

ROENTGEN-RAY DOSAGE

Again, unfortunately, we have not found any magic dose of roentgen rays which can be relied upon with certainty to kill cancer. It is patently apparent that cancers differ in their susceptibility to roentgen rays. The various grades and types of cancer are so unreliable in their behavior that the value of any classification is limited. Since a reliable "tumor dose" is unknown, we did not try to use one in calculating the amount of treatment for our successful cases. We relied on the reaction produced by the "applicator dose" with the physical factors of the treatment set-up to determine the amount of radiation given in each case. The applicator dose is the actual amount of radiation given off by the apparatus used. It is an amount which can be simply and accurately measured. It is the basic dose from which all other types of doses must be calculated. The applicator dose for roentgen rays is expressed by roentgens in air, for radon seeds by millicuries implanted, and for the radon applicator by millicurie hours. When the applicator dose plus the physical factors of the treatment set-up are recorded, it is immediately apparent just how much radiation has been given. With such information a successful dose can be exactly repeated or intelligently modified as required. A tumor dose must be derived (often with considerable error) from the applicator dose and is simply an approximation of the number of roentgens or rads received by a tumor, the exact location and extent of which can only be guessed at. We do not think the total amount of radiation received by the cancer is as important as the *point dose* received by the one or two cancer cells which absorbed the least radiation. More important yet is the understanding that the calculation of any dose of radiation should be recorded with a complete statement of all the factors contained in the applicator dose. These respective factors can each vary widely and still by a proper combination produce the same "tumor dose." Often the radiologist or physicist calculates a tumor dose and omits a statement of these very factors. He simply states that the cancer received a certain number of roentgens or rads. Such a practice breeds confusion rather than clarity and simplicity.

Certainly, there is a place in the physics laboratory for the calculation of tissue doses in roentgens or rads. Such information may help in devising new and perhaps better ways of giving more effective radiation. In the meantime for the clinician the best measurement of radiation is still its effect on cancer.

ROENTGEN-RAY PORTAL SIZE

The volume of tissue irradiated is without doubt the most important single factor in the successful radiation treatment of cancer. The tissue volume must be relatively small. For example, when cancer-lethal doses of roentgen rays are administered through 6–7 cm. circular ports, the patients remain comfortable and in good health for years provided no local complications supervene. When the ports are increased to 8, 9 or 10 cm. in diameter, the number of successful cases decreases so that very few patients are found free of cancer

for five years, and those who are, are not all functionally satisfactory (due to fibrosis of soft tissue, stomatitis sicca, trismus, radionecrosis, etc.). We know how important it is to use ports of small size carefully centered over the cancer. This knowledge is the basis for our insistence on round or oval ports—both shapes in which all useless corners are eliminated and in which the volume of tissue irradiated is reduced by more than 20 per cent over square and rectangular ports of similar dimensions. Our disappointing experience with large ports has impressed upon us the futility of irradiating one whole side of the neck for metastatic cancer. We prefer neck dissection and reserve radiation for smaller well localized deposits of cancer. We have read many articles on therapy where the volume of tissue irradiated was not stressed or in many instances not even mentioned. In such reports it must be assumed that this vital factor was not sufficiently appreciated.

PALLIATION WITH ROENTGEN RAYS

There is still considerable confusion as to just what is meant by the term, palliative roentgen-ray treatment. How much treatment, to what area, for how long, palliates whom? For instance, we seriously question whether the use of roentgen-ray ports larger than 12 cm. is ever justified even in an effort to obtain palliation. Both the local and systemic dysfunction produced by even subcancer-lethal doses of roentgen rays given through large ports may be seriously harmful and sometimes rapidly fatal, proportionate, of course, to the dose administered. Better relief from the discomfort and pain of advanced cancer can often be secured by moderate doses of judiciously implanted weak radon seeds or by small doses of roentgen rays directed only to limited areas where the cancer is most active or painful.

LATE COMPLICATIONS OF SUCCESSFUL RADIATION THERAPY

Some of the bitterest and most discouraging aspects of otherwise successful radiation therapy are the complications of treatment which appear years later and are often as lethal as the original cancer. Unfortunately, the destruction of cancer with roentgen rays produces a varying degree of damage to normal structures as well; such damage is not static and tends to become progressively worse. Some patients, who are apparently controlled, return eight or nine years later with new cancers growing at the margin of a previous treatment area in tissue damaged by radiation. These lesions are probably radiation induced cancers and their control by surgery is discouragingly difficult. Radical surgery made in any area of advanced radiation damage is fraught with danger and many complications are to be expected, some even fatal.

Many successfully irradiated mouth cancers develop late osteoradionecrosis requiring removal of large portions of the mandible or maxilla, often more disfiguring and disabling than if the original treatment had been by surgery. Successfully controlled metastatic cancer in the neck is sometimes followed by late breakdown of the irradiated tissues, with exposure and then rupture of the carotid artery with all the danger inherent thereto. Radiation fibrosis in both sides of the neck has produced late bilateral vocal cord paralysis and dysphagia due to scarring around the vagus nerves. Such damage can convert the larynx into a useless and dangerous organ which must be removed to protect the patient from death by aspiration.

Experience with cases such as these tends to make one very thoughtful when deliberating the relative merits of radiation and surgery for the initial treatment of a new case.

CONCLUSION

Our own experience indicates that we have not yet found the ideal combination of physical factors for the successful irradiation of the various forms of head and neck cancer. Radiation therapy, in general, over

the past twenty years has been an increasing disappointment to many of us who held high hopes for its ultimate possibilities. An example is the almost complete ineffectiveness of roentgen rays in controlling cancer which has invaded bone or lymph nodes. Consequently, we must continue to treat patients by radiation methods which we know have succeeded in the past. We must modify, refine and try to improve these techniques from time to time as new ideas and new equipment become available. We must give preference to surgery in those cases in which the morbidity can be decreased and the salvage increased over the results of radiation therapy described in this report.

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The author wishes to acknowledge his indebtedness to Dr. Hayes Martin, under whose direction this clinical material was collected and whose original idea it was to present our radiation experience in somewhat this fashion. Without his guidance and wisdom gained through many years of practice in the irradiation of head and neck cancers, and which he has so generously imparted to the author on innumerable occasions, it would have been most unlikely that this report would have been made.

A STUDY OF RADIATION FAILURES AND THE ROLE OF RADIORESISTANCE IN THE TREATMENT OF CANCER OF THE CERVIX*

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DESPITE fifty years of radiation therapy for cancer of the cervix, an acceptable cancerocidal dose for this disease has not been defined. A dose simply expressed in units of radiation delivered in rads or roentgens is well known to be inadequate. This is because the biologic response of tissue to irradiation is dependent on much more than the total roentgens delivered. A variety of factors are known to influence this biologic response and have been described. Many others are still unknown.

The many factors now recognized to influence the biologic response may be divided into two groups. One group includes those traits which are inherent or dependent on the tumor itself. The second group consists of those factors associated with the administered therapy. The former group is represented by such entities as the gross microscopic characteristics of the tumor, presence or absence of infection, mitotic rate, blood supply, and oxygen tension within the tumor. This is not intended to be a complete list, for at present many more are known and more are apt to be added in the near future. But, for the purposes of this presentation, these will suffice to denote the aspects to which we allude. Probably the most important factor of the second group is the intensity of irradiation, or the time-dose relationship, and this includes fractionation and protraction.

Modification in any one of the aforementioned features is capable of influencing the biologic response of a specific tumor, all other factors remaining equal. The experienced radiotherapist has learned to take advantage of this characteristic and under certain conditions, or in the presence of certain of these features, will modify and alter the time dose relationship to obtain optimal results. At present this qualification is an empirical one for there is no way of totaling the individual agents present in any one situation in such a way as to allow the prescription of a minimal dose and time factors which will guarantee the eradication of a tumor. There is no formula which equates all the features of the tumor to the therapy factors, nor are there any specific rules which will allow compliance for the changes.

Observation of many cases, however, has led to certain determinations which, in general, are the physical measurements seemingly necessary to control cancer and the definition of a range of dosage within which the majority of the cases fall. As an example, Strandqvist[10] has plotted a curve which does just this for carcinoma of the skin. The data were assembled many years ago and relate only to squamous cell carcinoma of the skin. There has not been any comparable study for carcinoma of the cervix. Neither has there been any demonstration of the validity of this curve for carcinoma of the cervix. Nevertheless, because of the fragmentary evidence of its analogous value in relation to cervical cancer, coupled with the lack of anything better, it has come to be generally accepted as satisfactory. A comparable study of this nature for carcinoma of the cervix is of the utmost importance and a necessity at the present time.

In the mechanics of treatment for cervi-

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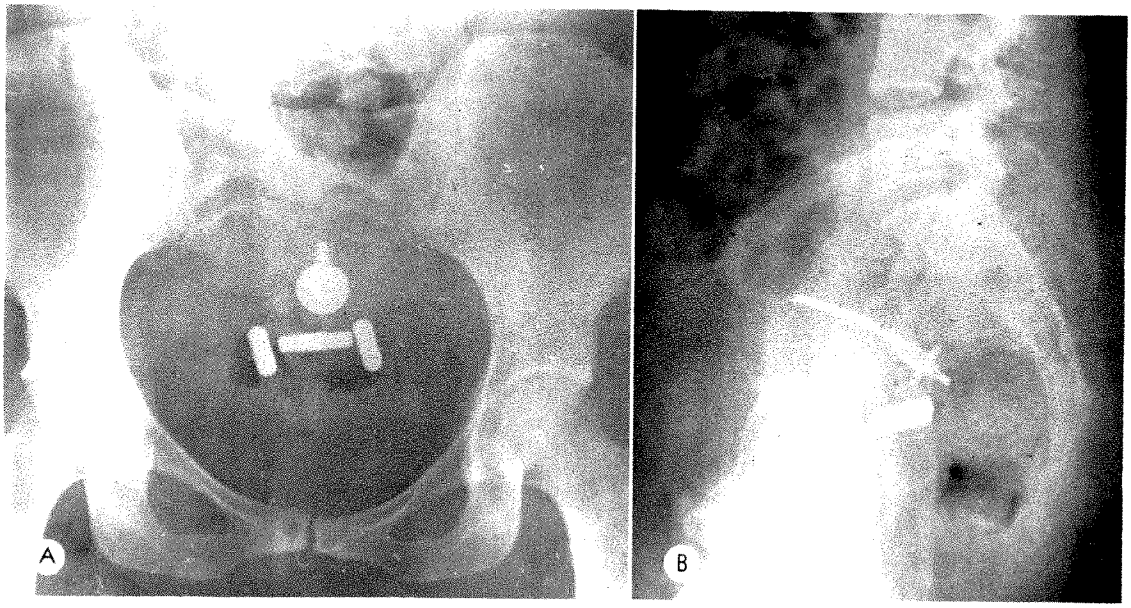

Fig. 1. (*A* and *B*) Case I.

cal carcinoma, an attempt is made to deliver at the minimum a cancerocidal dose to the cervix. In actual practice because of the endeavor to increase the dose to the lateral areas of the pelvis, a dose much in excess of an acceptable cancerocidal dose is administered to the cervix and adjacent vagina. A safe dose for this area would be a tolerance dose to the rectum, bladder and point A as described by Tod and Meredith.[11,12] In summary, therefore, an attempt is made to deliver a maximum dose to the pelvic structures within their tolerance, and, in so doing, it is reasonable to expect that the cervix and adjacent vagina will receive a dose in excess of the cancerocidal dose. As an outcome of such practice and reasoning, it has been accepted that a satisfactory dose to the cervix would be supplied by the use of radium applied in the form of a uterine tandem and vaginal ovoids over a period of four to five weeks and in one to three applications for 5,000 to 8,000 mg. hr. (depending on the type of colpostat used). Although we recognize the wide range of biologic responsiveness due

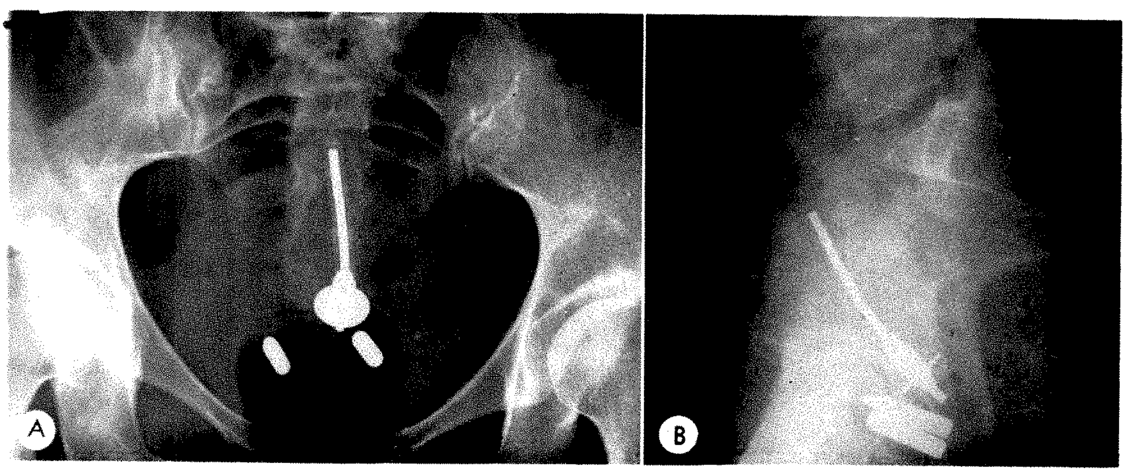

Fig. 2. (*A* and *B*) Case II.

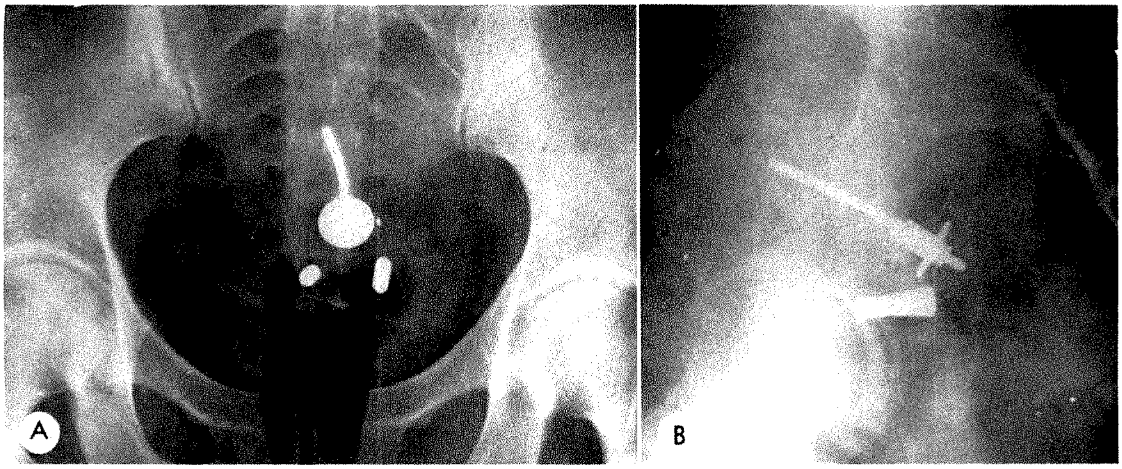

Fig. 3. (*A* and *B*) Case III.

to different factors, both in the tumor and the applied therapy, there is a generalized therapy dose which should encompass these variables and yield successful results.

The eradication of a cancer of the cervix by irradiation implies that a dose was delivered to all tumor bearing areas of sufficient magnitude and intensity to cause directly, or indirectly, the destruction of the cancer. Conversely, therefore, it may be said that failure to obtain such eradication implies that the necessary dose was not delivered.

A physical feature of radiation is that the intensity varies inversely with the distance from the source. Because of the anatomy of the pelvis and the direction of spread of the cancer laterally within this anatomic framework, there are areas in the lateral parts of the pelvis which are relatively removed from the radium sources. Staying within the confines of tolerance dosages allows for the fact that there will be areas in the lateral parts of the pelvis which fall beyond the effective range of irradiation. Therefore, it may be argued logically that the failure to eradicate cancer in the lateral parts of the pelvis is directly due to the inability in certain cases to deliver adequate cancerocidal doses of radiation as defined above. This has been borne out by many studies[8] in

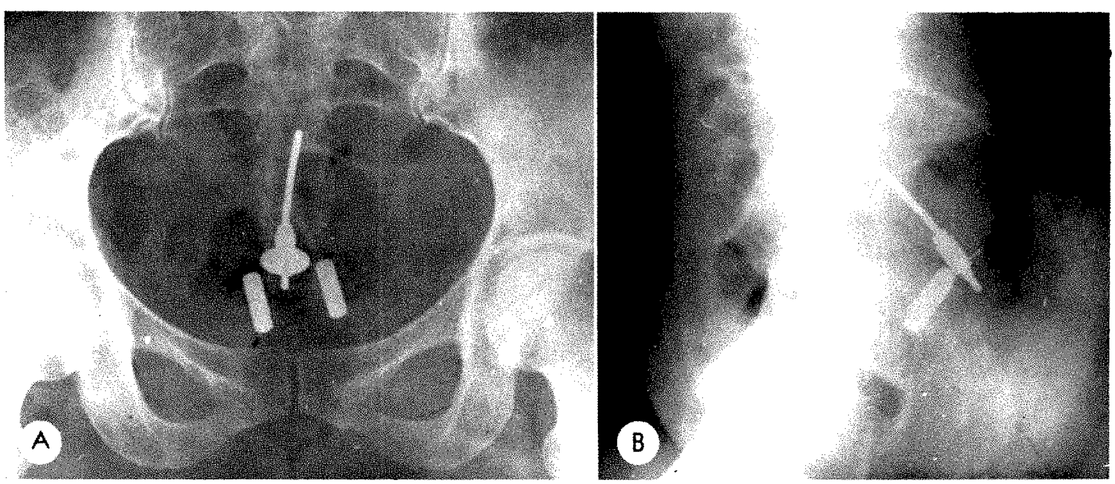

Fig. 4. (*A* and *B*) Case V.

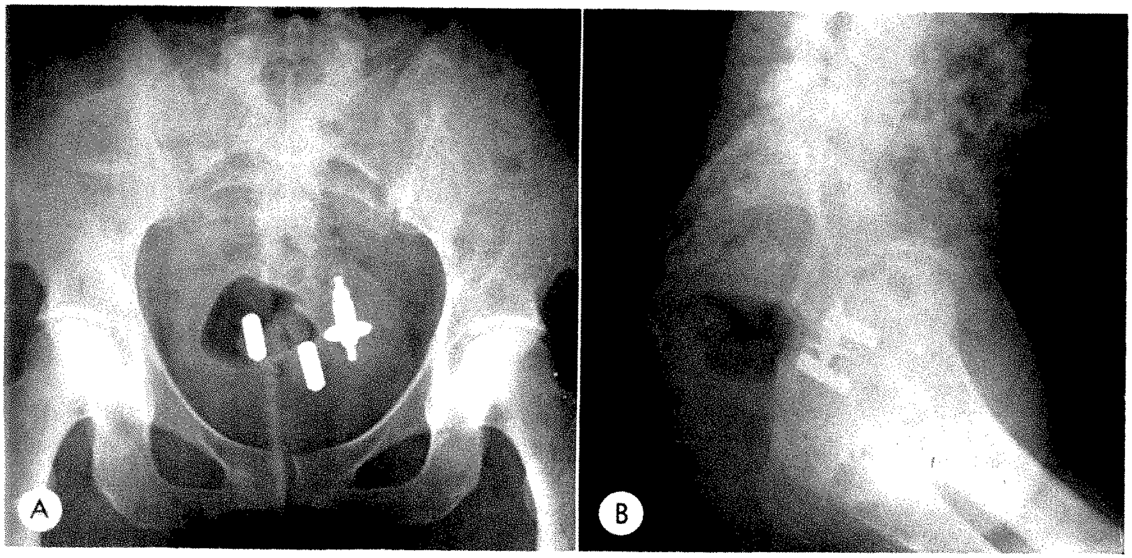

FIG. 5. (*A* and *B*) Case VI.

which attempts were made to measure the total doses delivered to the parametria.

However, the primary site of the cancer at the cervix and within its immediate periphery is so readily accessible to the radium that it would be extremely rare to anticipate an inability to deliver to the cervix a dose of radiation within the wide scope of the acceptable range. It is this very notion which probably accounts for the factor known as radioresistance of cervical cancer. The unexplained persistence of a cervical cancer after its irradiation with an adequate dose and by a method which should prove successful is why such cancers are quite apt to be labelled "radioresistant." This is substantiated by the frequency with which the term appears in the recent literature dealing with cervical cancer, and for this reason there has been an impetus in the resurge of surgical procedures for these cases. By the same token great furor in the search for techniques and means by which to define and diagnose the presence of cervical cancer prior to treatment by irradiation has been

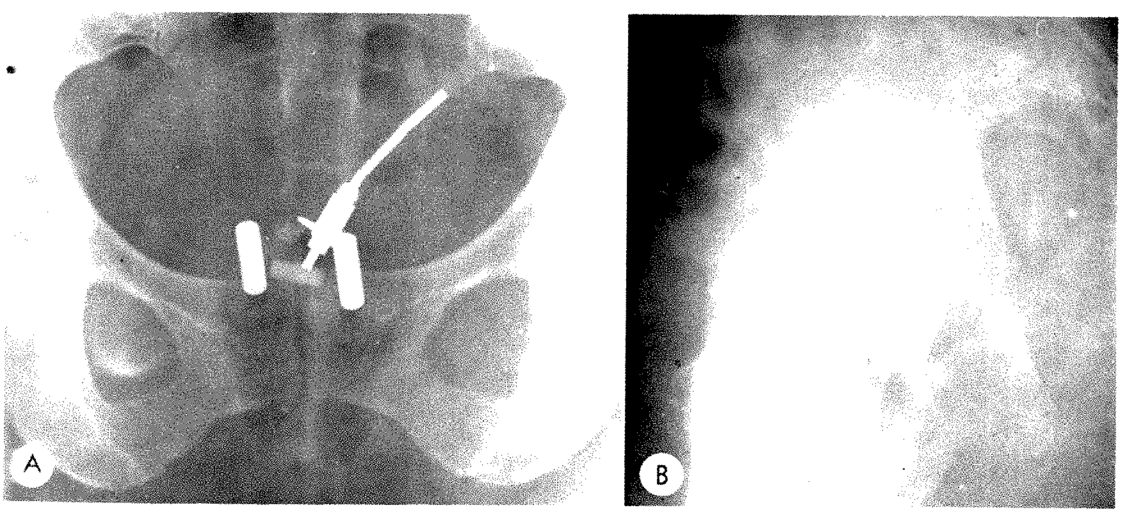

FIG. 6. (*A* and *B*) Case VII.

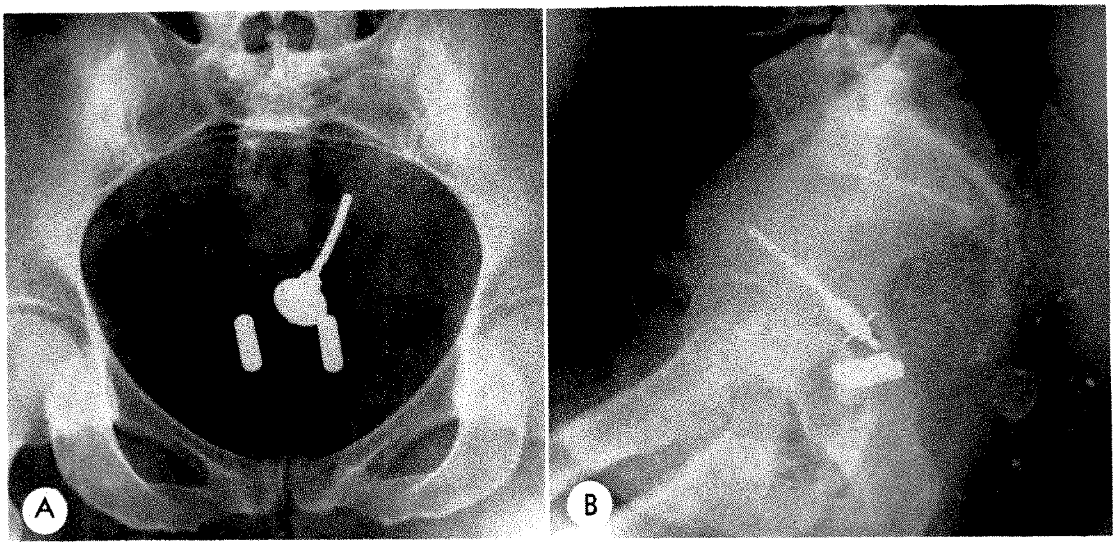

Fig. 7. (*A* and *B*) Case VIII.

created. Granted that such a designation in the face of what is considered adequate therapy under otherwise normal conditions is extremely tempting, it, nevertheless, behooves us to carefully re-evaluate our acceptance of it so readily.

In simple terms, absolute radioresistance does not exist. Any tissue, normal or malignant, can be destroyed if enough radiation is applied. Radioresistance in therapy is really the relative resistance of normal versus cancerous tissue. This relative sensitivity of various tissues is the very essence on which radiation therapy is based. It must be recognized that the term radioresistance as it is designated here refers only to the relative sensitivity of tissues within the limits of toleration of normal tissues and therefore within the practical limits of applied radiation therapy.

MATERIAL AND METHOD

Attempts to correlate the "radioresistance" of a cervical tumor, prior to its

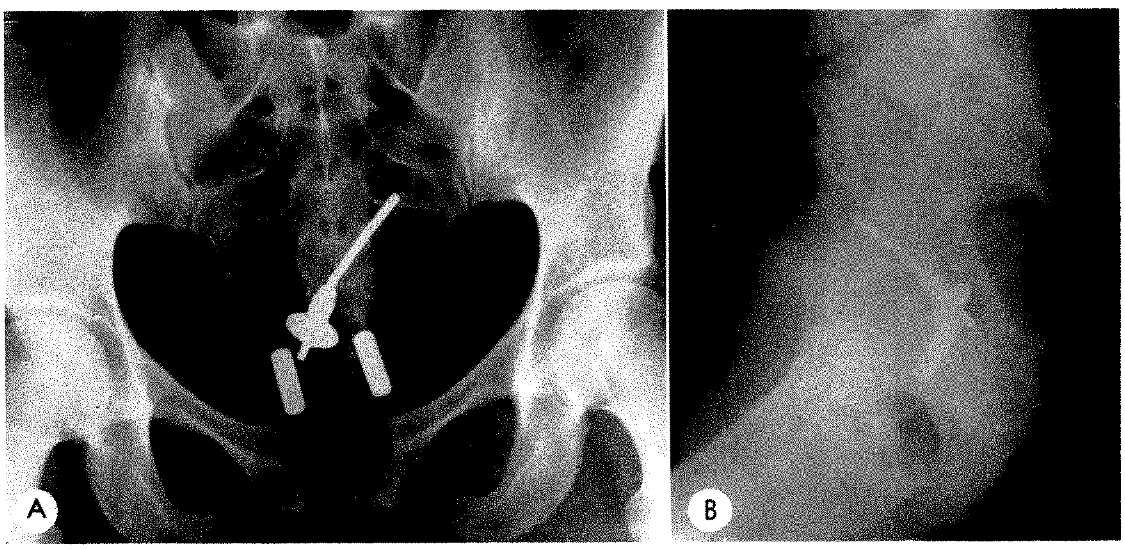

Fig. 8. (*A* and *B*) Case IX.

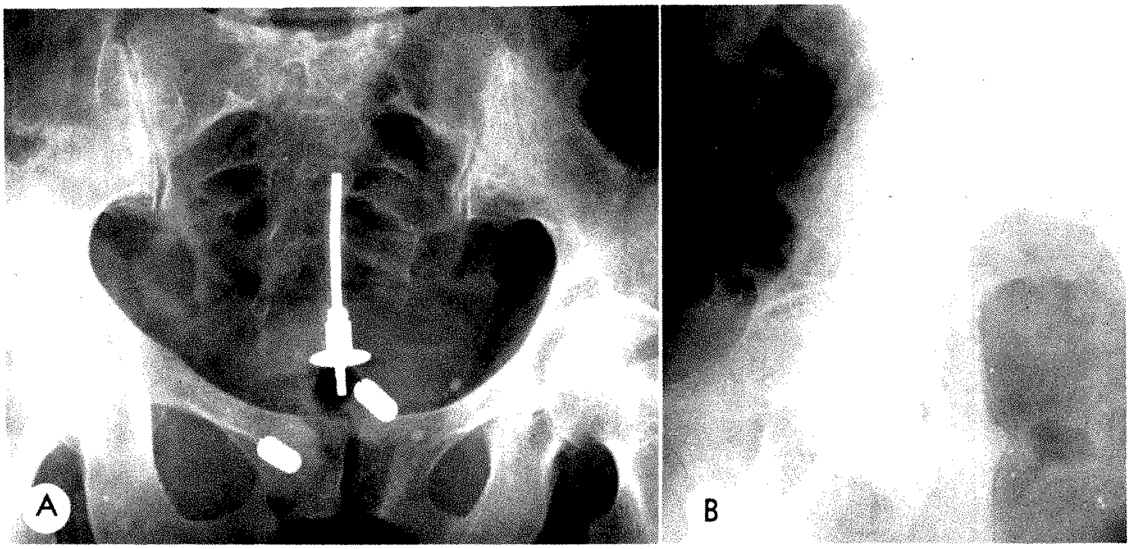

Fig. 9. (*A* and *B*) Case xii.

treatment by irradiation, with the actual end results have not been successful in our hands. The three methods utilized in this endeavor included: first, a correlation of the histologic-grading using Broders'[2] classification with the tumor response; secondly, attempted correlations of vaginal smears and tumor response prior to treatment as described by Graham and Graham;[5,6] and thirdly, the method described by Glücksmann and Way[3,4] of studying the modification of cell types after small amounts of irradiation. No valid correlations were obtained with these three methods. A review of the literature shows that there is a similar lack of confirmation by others of the value of such tests.

The insignificance of radioresistance as a

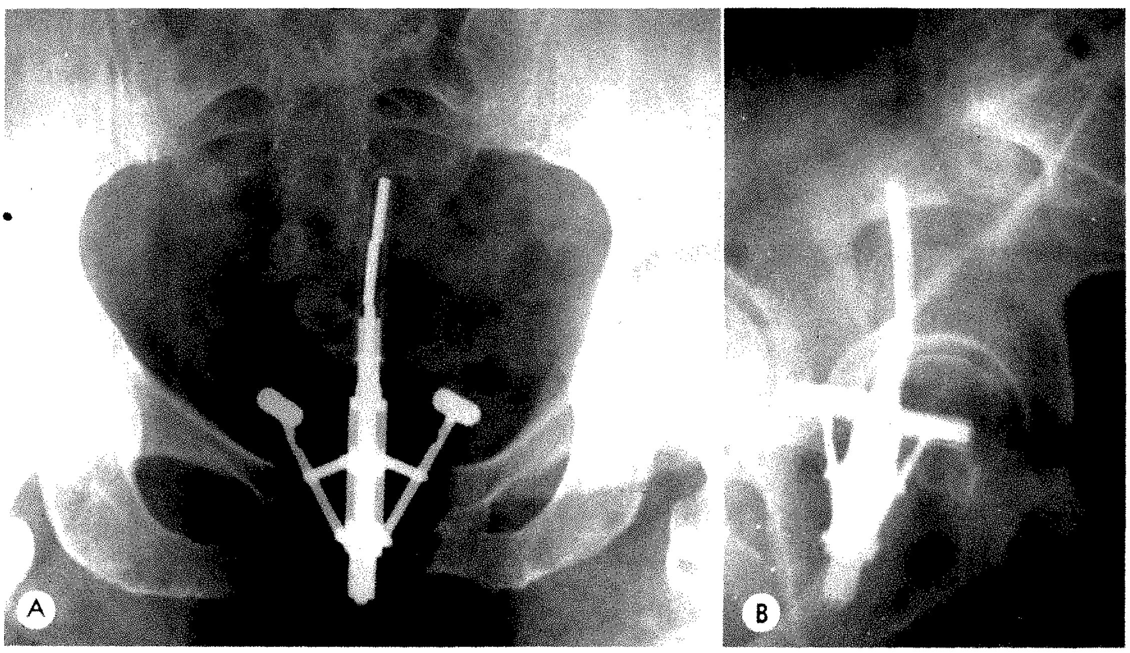

Fig. 10. (*A* and *B*) Case xiii.

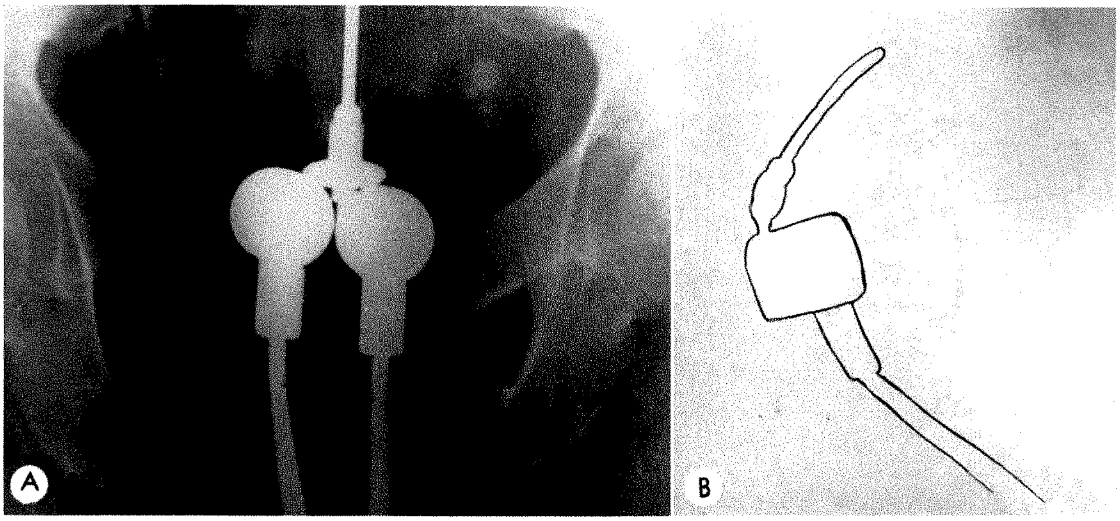

Fig. 11. (*A* and *B*) Case xiv.

cause for failure of radiation therapy became evident when we began to carefully re-evaluate the failure cases treated since 1950. During the years 1950 to 1956, a total of 422 cases of primary carcinoma of the cervix, Stages I, II and III were treated at the Washington University Clinics. Table I is a compilation of the results.

A review of the 124 failure cases revealed that a total of 14 patients died of distant metastases without pelvic involvement. By far, the majority of failures occurred in the group with persistent disease in the pelvis. Of these only 23 had persistent disease locally at the cervix and vagina; the other 87 cases were failures of treatment due to

Table I

carcinoma of the cervix 1950–1956
stage I, II and III

Alive and well	268
Dead of intercurrent disease	13
Lost to follow-up	17
Distant metastases without pelvic involvement	14
Persistence of carcinoma at cervix or vagina	23
Persistence of carcinoma in pelvis without involving cervix or vagina	87
Total	422

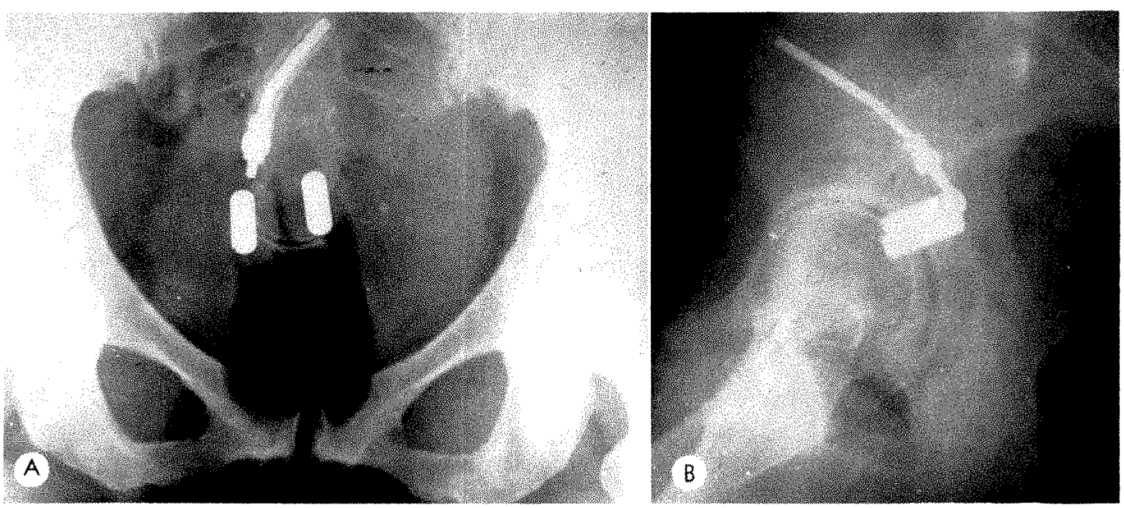

Fig. 12. (*A* and *B*) Case xv.

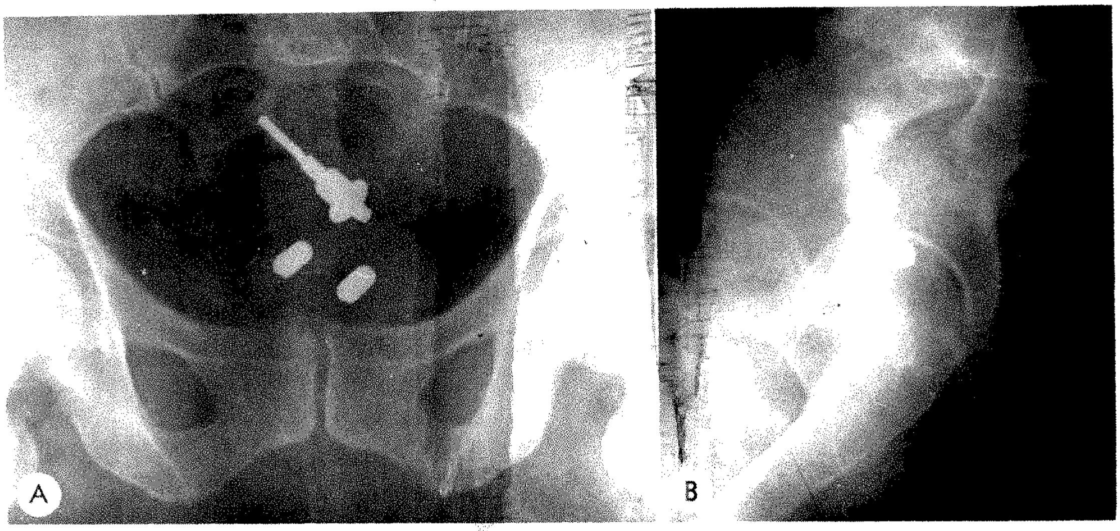

Fig. 13. (*A* and *B*) Case xvi.

persistence of disease in the lateral pelvis with or without associated distant metastases.

It would be unreasonable to consider all these failure cases as due to radioresistance. Certainly, the group of patients who died of distant metastases without local recurrence cannot be included. In the same way it is believed unlikely that failures in the group of patients who died with disease in the lateral pelvis not involving the cervix and its immediate confines were due to radioresistance. The anatomic and physical factors involved might have been such as to make it impossible to deliver a dose of radiation to the lymph node areas comparable to that received at the cervix. It would be more reasonable to assume that these failures were due to underdosage, particularly when the radiation was successful in eradicating the local lesion.

It would not be out of line, however, to assume that failure to achieve eradication locally at the cervix was due to radioresistance. Therefore, the 23 cases listed as having persistent cancer of the cervix, or

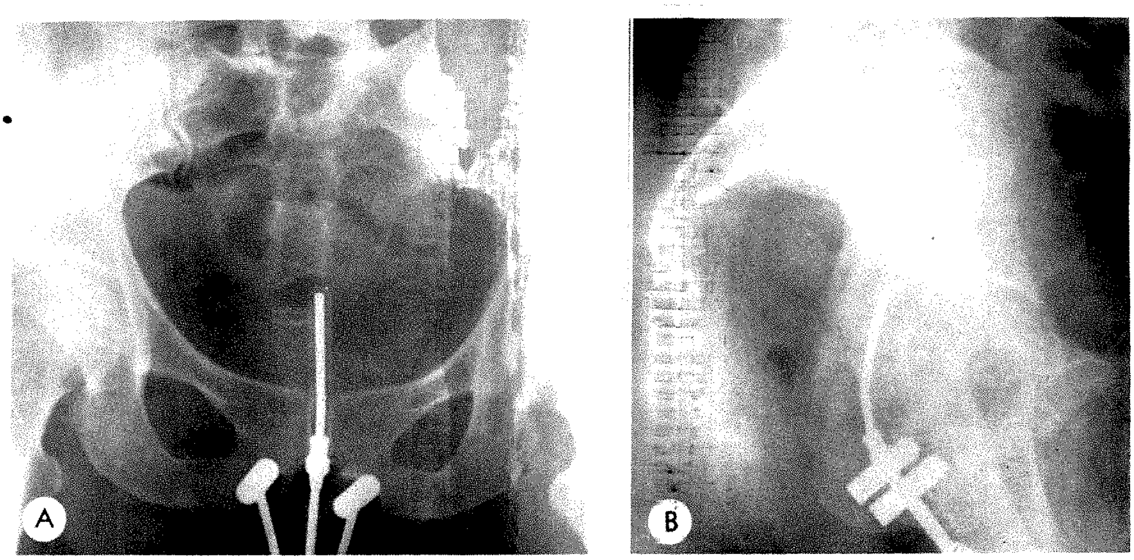

Fig. 14. (*A* and *B*) Case xviii.

within 2 cm. of the midline or the upper vagina, with or without disease elsewhere, could be termed radioresistant. Nevertheless, we must consider one other possibility. The application of radium is sometimes difficult because of the anatomic features of the cervix, vagina and the tumor. An assumption that the procedure has been accomplished satisfactorily because it so appears at the time of packing is not necessarily so. A critical appraisal of radium application procedures performed during the last ten years convinced us of the great care and effort necessary to obtain completely satisfactory insertions. Before considering all of these 23 cases as failures due to radioresistance, it was necessary to determine whether the intended dose was delivered. To do so, the 23 failure cases were re-evaluated. Roentgenograms were available for study in only 18 of these cases. The doses delivered to various points in the pelvis and particularly the areas of recurrence at the cervix, fornices, or immediate parametria were recalculated as best as possible from the roentgenograms of the radium applications and associated factors. The site of recurrence was estimated as best as possible on the roentgenogram. Measurements from the end or center of each of the radium tubes to the site of recurrence were carried out. Corrections for magnification of the roentgenograms were made. Dose tables[9] were used to define the dose that each tube of radium delivered to this point and the totals were calculated. A comparable point on the opposite side was similarly defined and the dosage at this point also was calculated on the same basis. The findings are of particular interest.

In Table II the significant data relating to each failure case are listed. Roentgenograms of the 18 cases which were available are reproduced showing one typical application from two or three that might have been made for each case (Fig. 1–18). The majority of these applications were done with separate intrauterine tandems and vaginal ovoids. In general, the Manchester system[7] of distribution was attempted. The tandems usually contained sources of 20–10–5 mg. of radium in that order from the top, and the ovoids contained 20–20 mg. sources. At first glance it may seem impossible to obtain discrepancies of the order shown in the table. However, if one recalls the isodose curves surrounding radium sources and considers the proximity of these sources to the cervix and the upper vagina, distances as short as 1 cm. may cause tremendous differences in the doses received by the tissues. This is particularly so when the error is compounded by derangement in both the tandem and the ovoids. Obviously, in retrospect none of these applications were satisfactory. Since in most of the cases a separate tandem and ovoids were used, it was often difficult to align the sources accurately in relationship both to each other and to the cervix and tumor. Ideally, their distribution should produce a uniform isodose pattern in the pelvis. This does not imply that fixed tandem-ovoid applicators are faultless. Though the relationship of tandem and ovoids to each other is maintained, other mistakes do occur.

In several of the failure cases, it became obvious that the radium colpostat was allowed to remain in too low a position or too far from either the cervix or the fornices, most often because of failure to recognize or locate the cervix or upper vagina on the roentgenogram. Even though a uniform isodose pattern was produced, it still resulted in unrecognized low dosages at the tumor site. Similarly, the lowermost tandem source was at times too high above the level of the ovoids when widely separated. In these instances the resultant isodose pattern did not contain the tumor within its cancerocidal levels. With our present day experience, none of these would be tolerated and either would be corrected satisfactorily or other means to deliver adequate radiation would be sought.

In the hope of avoiding any such future errors, the present procedure for radium application is carefully planned. All pa-

TABLE II

RADIATION TREATMENT FAILURES

Case	Patient	Age	Stage	Year Treated	Recurrence (mo.)	Radium Treatments: no. of applications	Radium Treatments: no. days apart	Radium Treatments: total mg. hr.	Supplemental Treatments, roentgen therapy: r	Supplemental Treatments, roentgen therapy: no. of ports	Dose at Area of Recurrence (r)	Dose at Comparable Area on Opposite Side (r)
I	E.P.	34	I	1950	18	2	14	7,225	2,400	4	3,960	20,768
II	V.S.	59	I	1950	34	2	12	5,500	1,600	6	4,050	16,350
III	M.P.	56	II	1950	30	2	14	6,850	2,400	6	4,500	22,660
IV	M.F.	35	II	1950	11	2	26	5,440	1,600	4	No roentgenograms available	
V	C.S.	42	III	1951	10	2	28	6,400	2,700	6	4,150	17,470
VI	S.D.	46	II (stump)	1951	46	2	14	5,900	2,400	6	4,800	21,100
VII	L.B.	49	II	1951	11	2	21	7,410	2,400	4	5,455	10,675
VIII	F.C.	48	III	1951	10	2	14	6,590	2,800	4	4,765	17,025
IX	L.H.	36	II	1951	12	2	8	5,330	2,400	6	5,340	14,230
X	L.W.	43	II	1951	9	2	17	5,575	2,400	4	No roentgenograms available	
XI	L.B.	29	II	1952	7	2	21	6,640	2,400	4	No roentgenograms available	
XII	G.J.	67	I	1952	12	2	8	7,200	2,400	4	4,840	5,400
XIII	F.W.	63	II	1952	20	2	28	9,000	2,200	6	7,064	7,740
XIV	M.D.	67	III	1953	14	2	20	5,150	3,200 2,000	2 4	5,070	20,320
XV	C.N.	53	III	1953	11	2	14	7,100	2,400	4	4,980	18,030
XVI	L.C.	34	III	1953	12	3	40	8,100	3,200	6	6,360	14,412
XVII	R.S.	35	III	1953	4	2	14	6,820	2,400	4	No roentgenograms available	
XVIII	D.M.	55	II	1954	14	2	27	7,950	140 mc Au^{198}		7,418	7,278
XIX	A.R.	49	I	1954	11	2	21	7,625	140 mc Au^{198}		7,140	7,480
XX	G.S.	69	III	1955	22	2	14	8,700	130 mc Au^{198}		6,000	16,790
XXI	J.P.	47	I	1955	8	2	10	7,430	130 mc Au^{198}		No roentgenograms available	
XXII	H.A.	39	III	1956	17	3	34	9,800	140 mc Au^{198}		6,120	6,400
• XXIII	L.K.	59	III	1956	24	2	27	8,600	120 mc Au^{198}		6,480	6,480

tients are anesthetized and under completely sterile precautions the radium is inserted. The cervix is tagged by one or two silver vascular clips, which are clamped on a catgut suture and fixed in place. We have found this to be more satisfactory than direct clipping, since clips are apt to fall off, start bleeding or traumatize the tumor. After the radium is inserted, direct measurements with a scintillation counter[1] are made at the cervix and vaginal fornices. After packing the colpostat in place, measurements are also taken in the bladder and rectum, both midline and laterally. These measurements are extremely helpful in defining the adequacy of the application and the subsequent time exposures for the radium sources. Following this, anteroposterior and lateral roentgenograms are taken before the patient leaves the operating room and while still under anesthesia. The darkroom adjoins the operating room and within a few minutes roentgenograms are ready for review. If these are satisfactory, the patient is taken to the recovery room; if not, the necessary adjustments are

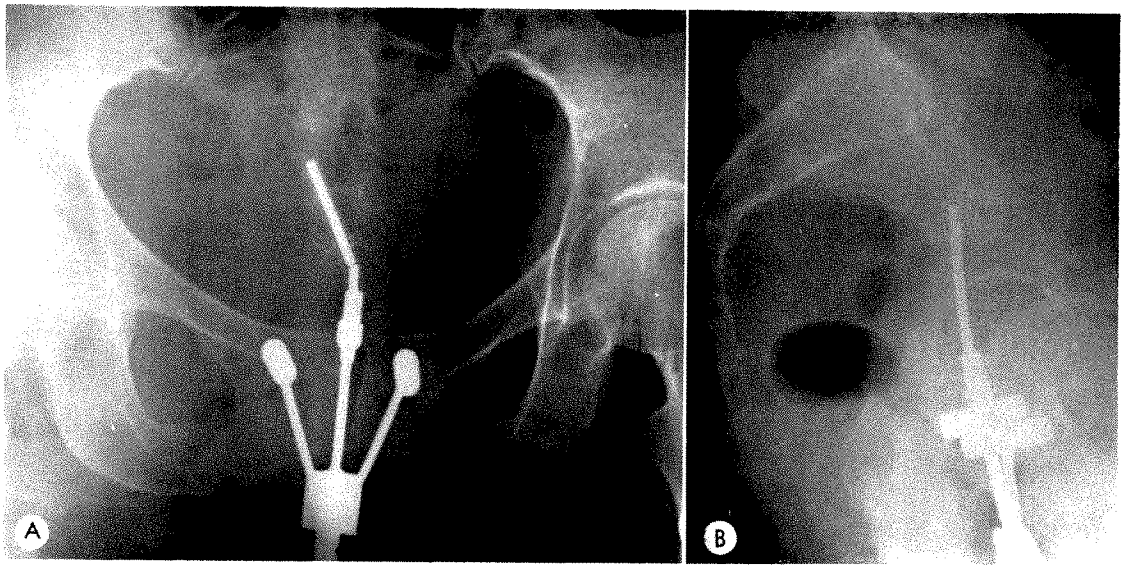

FIG. 15. (*A* and *B*) Case XIX.

made, even to the point of changing the entire colpostat, if necessary; repeat roentgenograms are taken until a satisfactory insertion is obtained. When the rentgenograms are dry, they are again reviewed and calculations of the dose at points A, B and cervix are made. The total exposure time is then determined.

In view of the findings, as shown in Table II, we cannot consider these 18 cases as failures due to radioresistance. If a dose level of 8,000 r is accepted arbitrarily as a minimal cancer dose, the cause of failure in all 18 cases is evident. This dose cannot be considered excessive. It can be delivered with relative ease to the entire cervix and upper vagina by intracavitary radium. It is not intended to belabor and stress the point of numerical dosages. The many factors which enter into radiation success have been discussed already. Assuredly, there are several cases in the successful group in which the measurements and insertions were in the same range as those

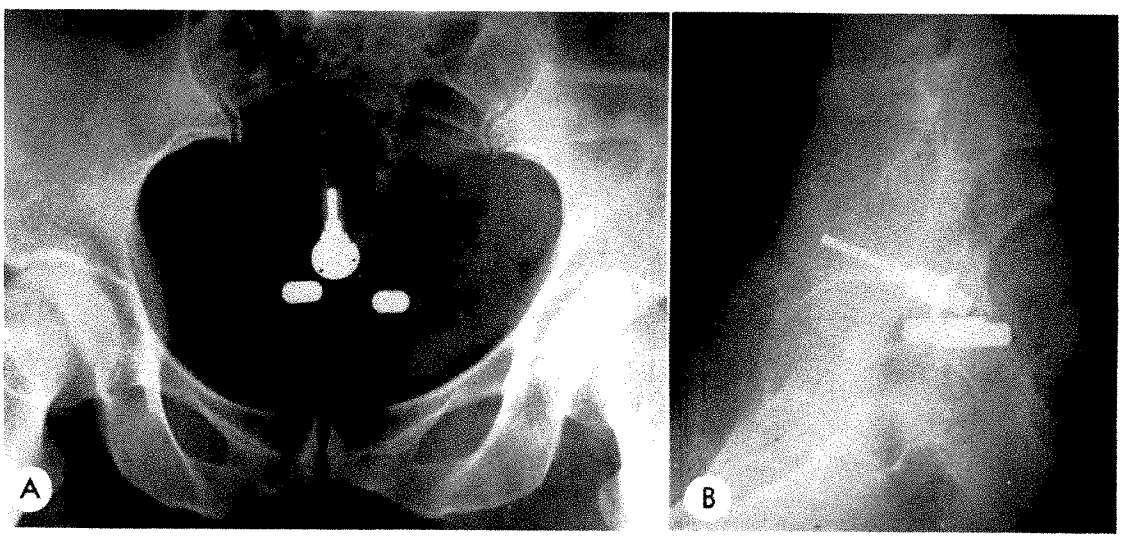

FIG. 16. (*A* and *B*) Case XX.

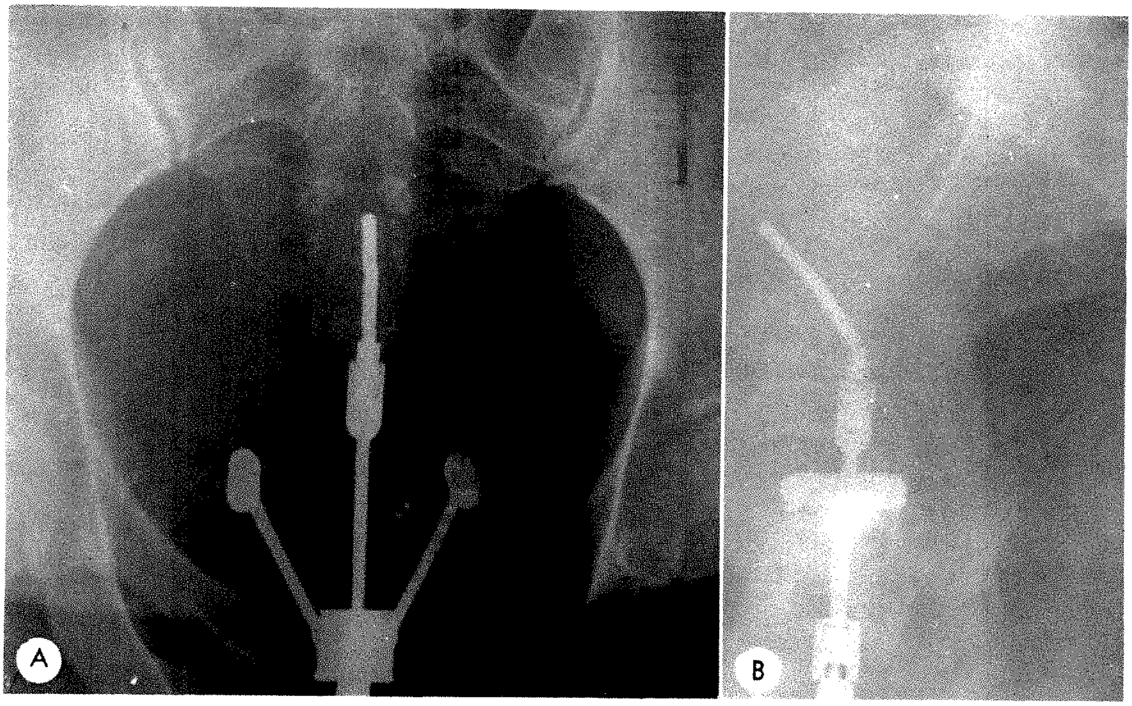

Fig. 17. (*A* and *B*) Case xxii.

in the failure cases. The difference probably lies in the fact that these were either extremely sensitive tumors or cases in which no tumor existed at these particularly low dosage points. It may be said that some factors were in operation which made possible the eradication of the tumor at these dose levels.

There is, of course, no certainty that higher dosages would have altered the subsequent course of the failure cases. It must be emphasized, though, that radiation failures did not occur when the dosage range was well within the practical limits of therapeutic techniques.

On the basis of our work, we feel that it

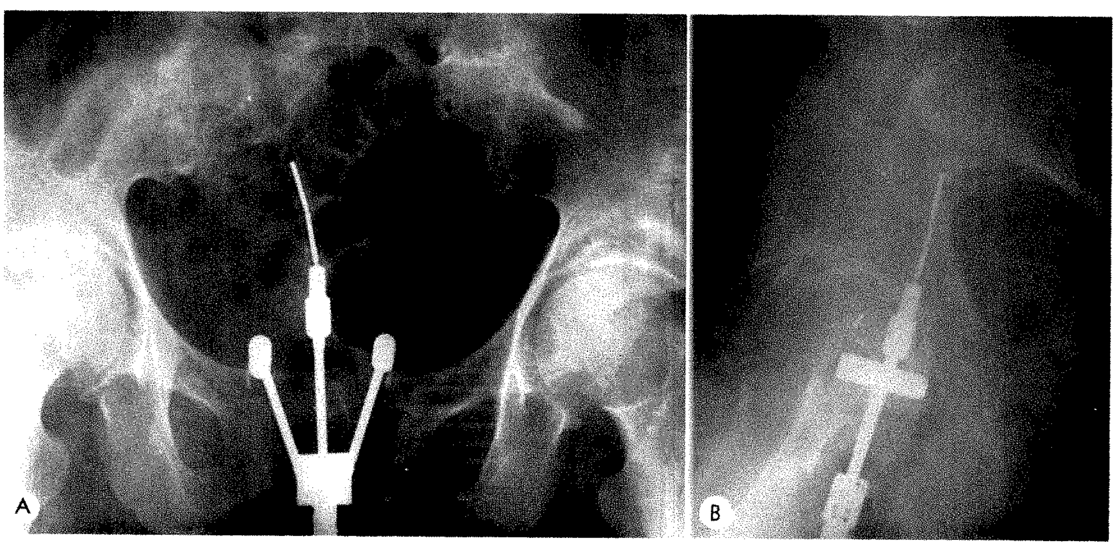

Fig. 18. (*A* and *B*) Case xxiii.

is necessary to modify our views regarding the subject of radioresistance. Before a tumor is regarded as radioresistant, inadequate therapy as the cause must be ruled out. More important, every possible means must be taken to avoid such errors in the future. The routine of a radium application must include all possible checks and to be accepted as satisfactory must meet the strictest criteria.

CONCLUSION

As a result of our experience we cannot accept the incidence of radioresistance in cancer of the cervix to be more than 1.2 per cent (5 of 422 cases). In all probability the incidence would be less if we were to appraise these additional 5 cases. The study shows the relative infrequency of radioresitance as the causative factor in radiation therapy failures. Such a low incidence does not deserve the attention that presently is being paid to it. Neither does it justify radical alterations in therapy, but rather helps emphasize the value of irradiation in the treatment of this disease. The ready acceptance of radiation failures as being due to radioresistance is a pitfall to be avoided. We believe that many cases are radiation failures not because of radioresistance but because of improper therapeutic techniques of the type indicated in our 18 cases.

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URETERAL OBSTRUCTION IN STAGE III CANCER OF THE CERVIX RELIEVED BY LOW INTENSITY RADIUM NEEDLE IMPLANTATION*

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THE importance of ureteral obstruction produced by parametrial invasion in cancer of the cervix with secondary uremia and infection was described by Chavannay[4] in 1899 and numerous similar articles appeared in the 1920's. Since both roentgen-ray and radium therapy were being used at that time, many were prone to attribute the ureteral occlusions discovered at autopsy to the fibrosis produced by these new methods of treatment.

HISTORICAL REVIEW

That such could indeed be the case was brought forcibly to our attention when a postmortem examination of one of our early patients revealed bilateral ureteral obstruction from radiation fibrosis with no demonstrable evidence of residual cancer of the cervix. Schmitz[18] reported a similar experience in 1920 and soon afterwards we started some studies aimed at the elimination of such serious sequelae. Dr. Fred Rogers, Professor of Physiology in the old Baylor Medical School in Dallas, offered to help with some experiments designed to determine the radiosensitivity of the ureter of the dog. His unusual skill as a dog surgeon enabled us to carry out this work with very few mishaps.

At that time we were attempting to control parametrial invasion with the implantation of monel steel needles, each of which contained 6.25 mg. of radium in an active length of 7.5 mm. and had a wall thickness of 0.35 mm., which permitted the emission of both beta and gamma rays. They were usually left in place for 8 to 10 hours. Of course, in the light of our present knowledge we know that the loading was too high, the filtration inadequate and the time too short but our technique was similar to that generally used in this country in the 1920's.

In the dog experiments, the left abdomen was opened and two of the steel needles were placed about 1 cm. apart on either side of the mid-left ureter for periods varying from 4 to 8 hours. Autopsies done 2 to 3 weeks later revealed complete ureteral obstruction and hydronephrosis produced by doses as low as 75 mg. hr. We were not capable of estimating these doses in roentgens when this work was done but recent calculations carried out with the help of Edith Quimby indicate that the combined beta and gamma radiation delivered to the ureter was somewhat in excess of 5,000 r. The details of this investigation were published in 1926.[7]

Some previous experiments, in which a 50 mg. well-filtered radium capsule was placed in contact with the ureter for 5 hours without producing serious damage, led us to believe that beta rays caused the ureteral strictures when the steel needles were used. With these data available, all steel needle implantations were discontinued and attempts were made to control ureteral obstructions secondary to parametrial invasion by various radium capsule and roentgen-ray techniques combined with ureteral dilatations, indwelling catheters, ureteral transplants, nephrostomies and ureterostomies. The results of this work, which produced marked palliation but no cures of long duration, were published in 1928.[9,10]

The use of radioactive sources in the parametria has always been intriguing because such a technique should enable the

* Presented at the Sixty-first Annual Meeting of the American Roentgen Ray Society, Atlantic City, New Jersey, September 27–30, 1960.

radiotherapist to limit a large dose to the affected region, thereby protecting such radiosensitive normal structures as the bladder and the bowel. In the early 1920's Burnam[2] and Levin[6] recommended the insertion of glass radon seeds through the vagina or peritoneum as a useful procedure. However, Levin noted a severe reaction in the tissues surrounding these implants and observed that many of the patients developed a high fever soon after they were inserted. Our experiments have led us to believe that even the seeds developed later, which provided a filtration of 0.3 mm. of gold or platinum, could not be used safely because they emitted some beta radiation.

More recently, radioactive isotopes have been employed for interstitial therapy. Allen, Sherman, and Arneson[1] report regression of malignant invasion of the parametria following the local injection of radioactive colloidal gold. Since beta rays constitute about 90 per cent of the radiation emitted by this substance, it seems logical to assume that ureteral, bladder and bowel damage should appear when injections are made near these structures. Carlin,[3] who has studied 22 patients with urologic symptoms from a series of 135 patients treated by Allen, Sherman and Arneson, believes that ureteral strictures and bladder injuries observed in at least 10 cases with no residual cancer could be attributed to the effect of the colloidal gold. He also believes that some of the patients with urologic damage were not included in his series because they went elsewhere for treatment or had so few symptoms from the ureteral obstructions that they were not referred for urologic investigation. The incrimination of a single method was found to be very difficult because all of the patients except 1 also received surgery, radium or roentgen therapy or a combination of these methods. Since beta rays penetrate only a few millimeters of tissue, the evidence presented suggests that stricture can be expected only when the colloidal gold is injected in close proximity to a ureter. The low incidence of such sequelae reported may result from the difficulty experienced in obtaining an even distribution of the injected material, particularly when the parametrium is infiltrated with carcinoma.

Obviously, the best form of interstitial radiation should be capable of destroying cancer cells while producing the smallest number of serious sequelae. In 1924 Regaud[16] postulated that such criteria could best be met by using very low intensity sources, heavy filtration allowing the emission of only gamma rays and relatively long treatment times. The so-called low intensity radium needles, which were first made available to us in 1930, have been found useful in carrying out such a plan of therapy.[11] They were used cautiously in the cervix and then in the vaginal walls and parametria. The good results reported by Pitts and Waterman[15] in 1940 encouraged us to use them more extensively and descriptions of our techniques were published in 1948[12] and more recently in 1957.[13]

Our conviction that low intensity radium needles could be implanted so as to produce no ureteral damage was substantiated by some experimental work published by Clayton[5] in 1951. He placed a platinum needle loaded with 2.4 mg. of radium in 4.0 cm. of active length on either side of the ureter in dogs for 168 hours and found no changes at the time of autopsy. The needle wall thickness was 0.5 mm.

TREATMENT

In a patient with a large cervical carcinoma complicated by a ureteral stricture produced by malignant invasion of the parametrium, treatment consists of a cylindrical implant of long needles in the periphery of the primary tumor often augmented by a long 25 mg. well-filtered capsule in the cervical canal and one or two vertical rows of similar needles in the involved parametrium. The radium remains in place for 7 days, except when the primary tumor is relatively small, in which event the central capsule is removed in 3 to 4 days or not used at all. Calculations made for some

such radium patterns indicate that point doses varying from 10,000 to 15,000 gamma r can be delivered to the parametrium in this manner and adequate doses can be given near the pelvic wall. Aside from a low grade temporary proctitis, very few sequelae have occurred and most of the patients have developed no persistent symptoms.

It is our belief that squamous cell carcinoma growing in metastatic nodes can be completely controlled only with doses of radiation larger than those used to eradicate the primary lesion. Experience has indicated that such nodes growing in the neck can be cured for long periods of time without irreparable normal tissue damage when such large doses are delivered with a combination of implanted low intensity radium needles and conventional roentgen therapy given while the needles are in place. In the neck, air doses of 350 r are given to a 10×10 cm. port daily until a total of 2,100 r has been reached, using conventional roentgen-ray equipment fully described elsewhere.[14] In the pelvis, air doses of 200 r have been given daily with an 80 cm. target skin distance to opposing 15×15 cm. anterior and posterior ports until 1,200 r has been delivered to each port while the parametrial needles are in place. The tissue dose of roentgen rays delivered to the midplane of the average pelvis in this manner amounts to approximately 1,400 r. In the more advanced cases this treatment has been repeated 6 weeks after the removal of the needles without producing any evidence of visceral damage.

REPORT OF CASES

The following case histories show that malignant parametrial invasion can be controlled and that in some cases ureteral obstructions can be relieved and renal function restored following the implantation of low intensity radium needles.

Case I (Fig. 1, *A* and *B*). This thirty-eight year old woman was admitted to the hospital complaining of a bloody discharge and severe pain referred from the right flank to the thigh for 3 months.

The blood sugar was 192 mg. per cent and she had an anemia. The cervix was hard, measured 4.0 cm. in diameter and was displaced to the right by parametrial infiltration which extended entirely to the pelvic wall. The biopsy report was squamous cell carcinoma, Grade III. An intravenous pyelogram revealed no obstruction of double ureters on the left side and no visualization on the right side.

The diabetes was controlled by medical treatment after which ten 2.4 mg. radium needles were placed in a cylindrical pattern in the periphery of the cervical tumor, one 2.4 mg. needle in the center of the mass and six 3.0 mg. needles in two vertical rows well out in the right parametrium for 7 days. While the radium was in place, 200 r (air dose) was given daily to each of two 15×15 cm. ports laid out over the anterior and posterior right pelvis for 6 consecutive days using 260 kv. equipment, a filter of ½ mm. of copper and 1 mm. of aluminum and a target skin distance of 70 cm. The patient was large and had a pelvic thickness of approximately 22 cm.

At six weeks the pain was almost completely relieved and she felt much better. The induration in the right parametrium was much less, the upper vagina was somewhat contracted and all visible evidence of carcinoma was gone leaving a gray radium reaction on the face of the cervix.

Intravenous urography done at 6 months visualized normal kidney pelves on both sides. However, the pleura on the right side was infiltrated with carcinoma and the patient died of generalized metastases at 1½ years with no demonstrable evidence of cancer in the pelvis.

Case II (Fig. 2, *A* and *B*). This sixty-eight year old woman was admitted to the hospital complaining of weight loss, weakness, low back pain and vaginal hemorrhage for 2 months. An intravenous urogram showed poor concentration of the opaque medium and bilateral hydronephrosis at 25 minutes. Pelvic examination revealed the cervix to be replaced by a friable bleeding tumor measuring 6 cm. in diameter and fixed in the pelvis by infiltration in both parametria extending to the pelvic walls. The biopsy report was adenocarcinoma.

Palliative therapy was undertaken by removing the presenting portion of the tumor by electrocoagulation and inserting eight 1.33 mg.

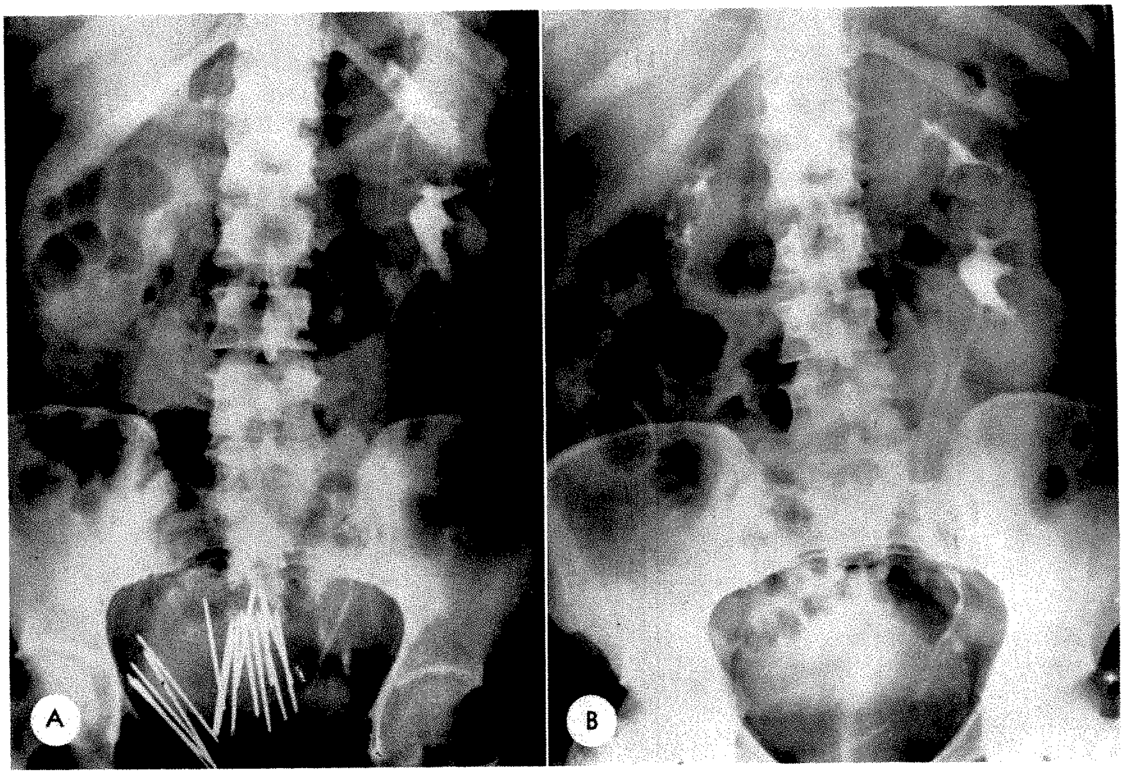

Fig. 1. Case i. (*A*) Nonvisualization of the right kidney pelvis and ureter due to ureteral obstruction secondary to malignant invasion of the right parametrium extending entirely to the pelvic wall. (*B*) Visualization of the normal right kidney pelvis 6 months after the implantation of low intensity radium needles in the cervix and right parametrium and the addition of a small amount of conventional roentgen therapy.

radium needles in the center and fourteen 2.4 mg. needles in the extreme periphery of the mass for 7 days.

At 4 months the symptoms were relieved and she had gained 15 pounds. The cervical mass was almost completely gone but induration could still be felt in the parametria. At 6 months the cervix was smoothly healed but she complained of some pain in the left groin. An intravenous urogram showed a normal kidney pelvis on the right side but the left pelvis was not visualized. However, a retrograde pyelogram made after inserting a catheter through a partial stricture in the lower left ureter revealed a moderate hydronephrosis on the left side. A course of roentgen therapy was given to the sides of the pelvis but the patient was then lost to follow-up.

Case iii (Fig. 3, *A* and *B*). This seventy-six year old woman was admitted to the hospital complaining of vaginal bleeding and pain in the lower back and hips for several months. Roentgenographic examinations revealed a solitary stone in the gallbladder, infiltration at the bases of both lungs and a hydronephrosis on the right side, demonstrated by a retrograde pyelogram. The cervix was very hard and large and was fixed by bilateral parametrial invasion. A metastatic tumor measuring 2.5 cm. in diameter was seen in the lower anterior vaginal wall just behind the ureteral orifice. A cervix biopsy was reported as squamous cell carcinoma, Grade ii.

A well-filtered 50 mg. radium capsule was placed in the cervical canal for 24 hours and ten 2.4 mg. radium needles were inserted in a cylindrical pattern well out in the periphery of the tumor of the cervix with four 1.33 mg. needles implanted longitudinally in the vaginal metastasis for 7 days.

At 4 months she felt much better and was free of all pelvic symptoms. At 6 months she still felt well except for weakness. A pyelogram indicated that the right kidney pelvis was normal. The vaginal tumor had healed and the upper vaginal walls were sealed over a small cervix. However, the liver was markedly en-

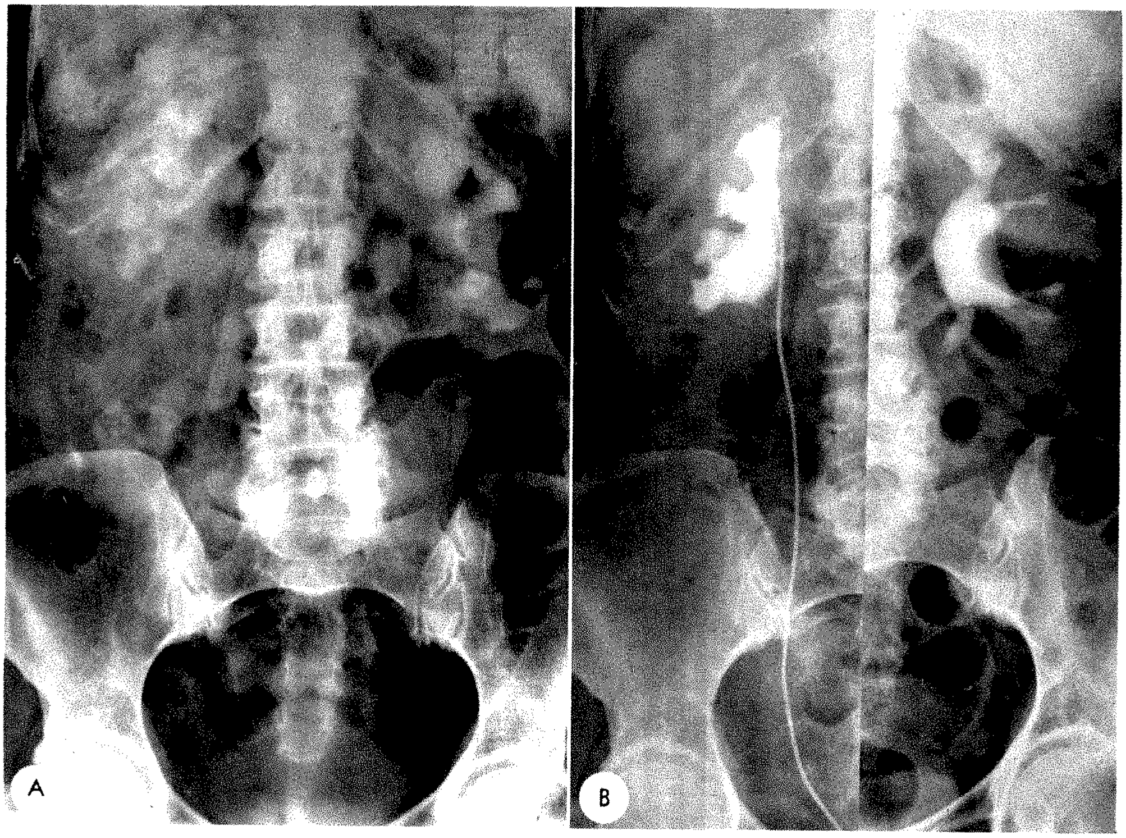

Fig. 2. Case II. (*A*) Obstruction of both ureters with poor visualization of moderately dilated kidney pelves secondary to malignant invasion of both parametria. (*B*) The condition is definitely improved at 6 months after low intensity radium needle implantation in a large cancer of the cervix and proximal parametria.

larged and the patient died of generalized metastases at 7 months.

Case IV (Fig. 4, *A*, *B* and *C*). This thirty-eight year old woman was admitted to the hospital complaining of right sided pelvic pain and postcoital bleeding of two months' duration. An intravenous urogram made by her urologist before admission revealed an obstruction low in the right ureter and a moderate degree of hydronephrosis. There was a double ureter and double kidney on the left side without evidence of hydronephrosis. The cervix was replaced by friable tumor tissue which extended to the right pelvic wall producing partial fixation of the cervix. The biopsy report was invasive squamous cell carcinoma.

Bleeding was controlled with electrocoagulation. Eleven 2.4 mg. radium needles were inserted in the periphery of the cervical tumor and four 3.0 mg. and one 2.4 mg. needles were inserted in a vertical layer well out in the right parametrium for 7 days. A dose of 200 r (air dose) was given daily to 15×15 cm. ports laid out over the anterior and posterior right pelvis on 3 consecutive days, following the radium needle implantation. The factors were 260 kv., a 70 cm. target skin distance and a filter of 0.5 mm. of copper and 1.0 mm. of aluminum.

On the fourth day roentgen therapy was stopped because the patient developed a pyelonephritis but the radium was left in place and antibiotic therapy was started. However, at 6 weeks she developed another attack of pyelonephritis and pyelograms done at home showed no improvement in the right sided hydronephrosis. A nephrectomy was considered but not carried out.

At 4 months she felt much better. The double ureters on the left side showed some dilatation but the pelves of both kidneys had a normal size.

At 1½ years she had gained about 38 pounds,

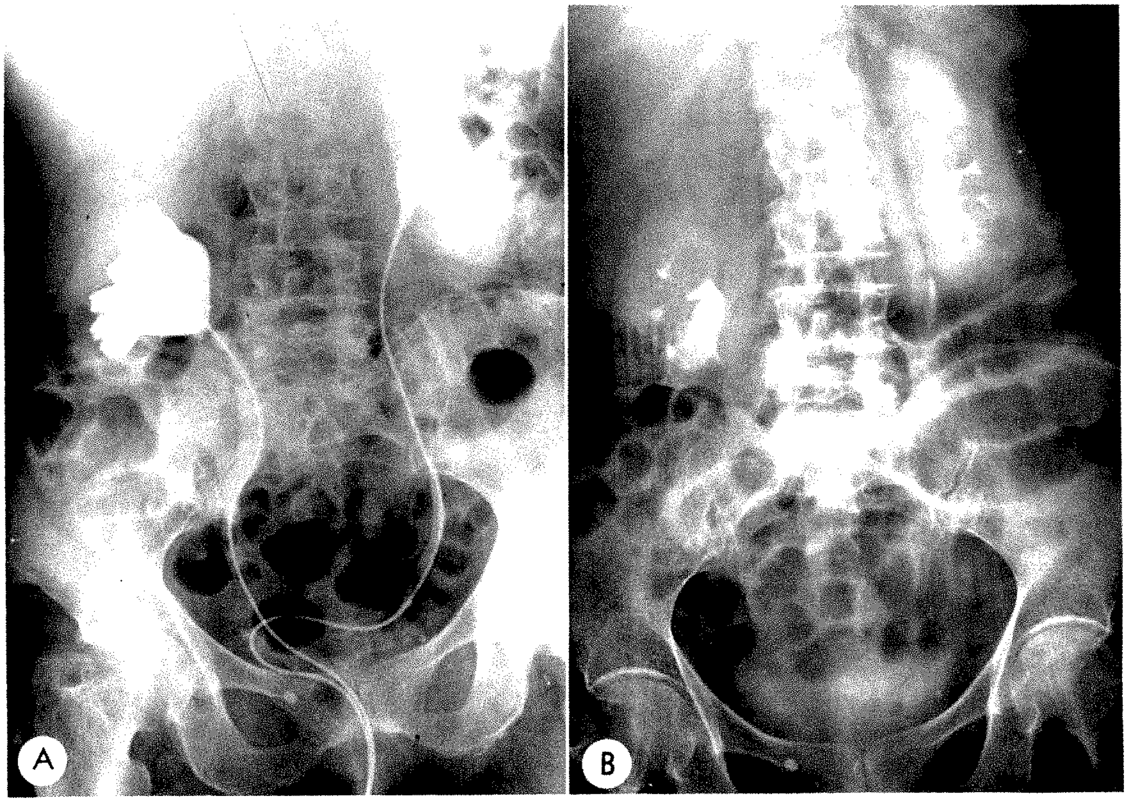

Fig. 3. Case III. (*A*) Obstruction of the right ureter with hydronephrosis secondary to malignant parametrial invasion is completely relieved (*B*) 6 months after the implantation of low intensity radium needles into a carcinoma of the cervix and the right parametrium.

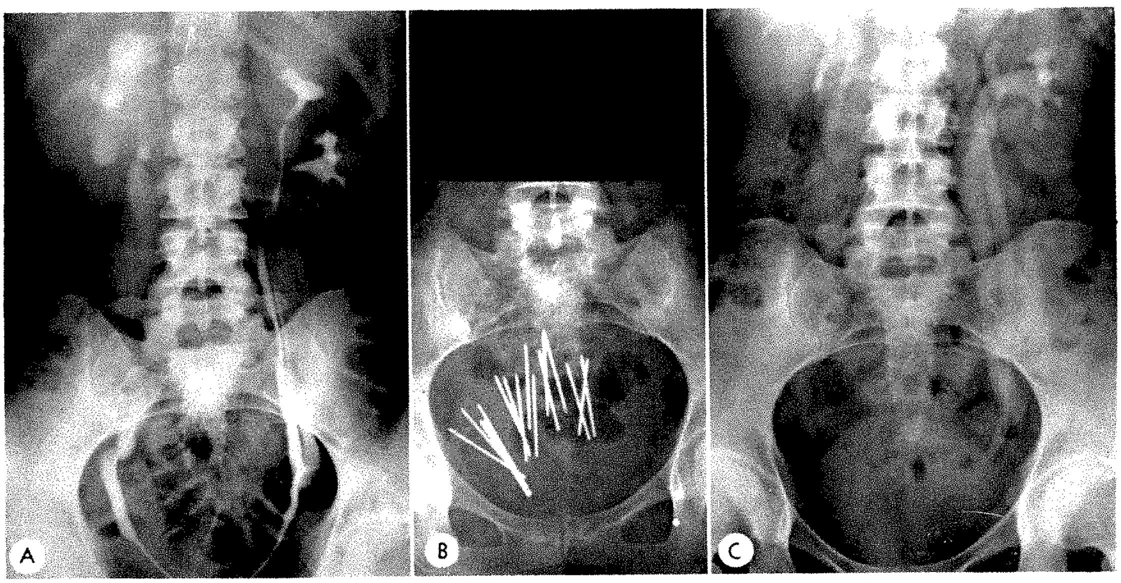

Fig. 4. Case IV. (*A*, *B* and *C*) Hydronephrosis and dilatation of the right ureter secondary to malignant invasion of the right parametrium was relieved in 4 months by the implantation of low intensity radium needles in a cancer of the cervix and the right parametrium for 7 days, with the addition of a small amount of conventional roentgen therapy.

had no pelvic symptoms and felt well. The kidney pelves still had a normal size and pelvic examination revealed no evidence of cancer.

Case v (Fig. 5, *A–D*). This forty-seven year old woman was admitted to the hospital complaining of repeated vaginal hemorrhages and severe pain in the right pelvis referred to the thigh of 12 months' duration. She received 4 blood transfusions before she was admitted and another one on the day of admission.

She was bleeding freely from a friable cervical mass which had invaded the adjoining vaginal walls and infiltrated the parametrium entirely to the right pelvic wall. The biopsy report was squamous cell carcinoma, Grade II to III.

The hemorrhage was controlled with electrocoagulation. Twelve 2.4 mg. radium needles were implanted into the periphery of the cervical mass, eight 3.0 mg. needles in two vertical layers in the right parametrium and a long two section 25 mg. radium capsule was placed in the lower segment of the uterus for 7 days. Roentgen therapy was administered daily to two 15×15 cm. ports laid out over the anterior and posterior right pelvis at the rate of 200 r (air dose) per port until 6 treatments were given. The treatment factors were 200 kv., a target skin distance of 80 cm., a filter of 0.5 mm. of copper and 1.0 mm. of aluminum. At the end of 6 weeks this roentgen therapy was repeated, thereby bringing the dose per port to 2,400 r.

At 3 months she was almost free of pain and felt much better. There was a small patch of radiation reaction on the face of the cervix but no visible evidence of carcinoma could be detected and the parametrium was soft. At 5 months a urogram showed the right kidney pelvis to have a normal appearance. At 9 months she felt well but a defect in the right ureter suggested the retroperitoneal extension of cancer above the original treated area and another course of roentgen therapy, adding 2,000 r to each of the two ports over the right pelvis, was given in 12 days.

At 16 months the right leg was swollen as a result of lymphatic blockage produced by radiation fibrosis in the right groin. At 17 months a small patch of radiation reaction in the posterior bladder wall was treated successfully by a urologist. At 3 years and 4 months she developed pain in the right pelvis when she was on her feet and a roentgenographic examination revealed fracture lines through both rami of the right pubis. Another examination done 2 months later showed callus formation about the fractures and the pain had disappeared. At 5 years she had no discomfort but walked with some difficulty because of the persistent swelling of the right leg from groin fibrosis. Pelvic examination revealed no evidence of carcinoma and a urogram showed normal kidney pelves.

Calculations indicate that the total dose of roentgen rays given to the midplane of the right pelvis during the year of treatment amounted to approximately 5,000 r. This therapy produced no internal damage but caused an induration in the subcutaneous tissues of the right groin with secondary lymphatic blockage. In the light of our present knowledge we believe that the results would have been as good if the third course of roentgen treatments had been omitted, thereby eliminating excessive fibrosis in the groin and swelling of the leg.

COMMENT

Since ureteral obstruction may be produced by external pressure as well as by direct invasion of the structures, it seems reasonable to assume that this complication might occasionally be relieved by conventional irradiation techniques. However, we have as yet been able to find very few such favorable results reported in the literature. Schewe[17] recently observed 5 cases that showed a disappearance of such strictures following roentgen therapy. A protracted series of intravaginal and external roentgen treatments was given to each case at the Ellis Fischel State Cancer Hospital during a period of 60 days. Three of these patients were living and well 9, 9 and 15 years later.

In a personal communication, Sherman states that he has seen similar results in a few of his cases treated with combinations of radium, roentgen rays, radioactive gold and surgery, but one finds it difficult to assign credit to the proper modality when such techniques are used.

SUMMARY

Dog experiments and clinical experience indicate that stricture of normal ureters can be produced by relatively small amounts of beta radiation, whereas cancerocidal doses may be used safely near the

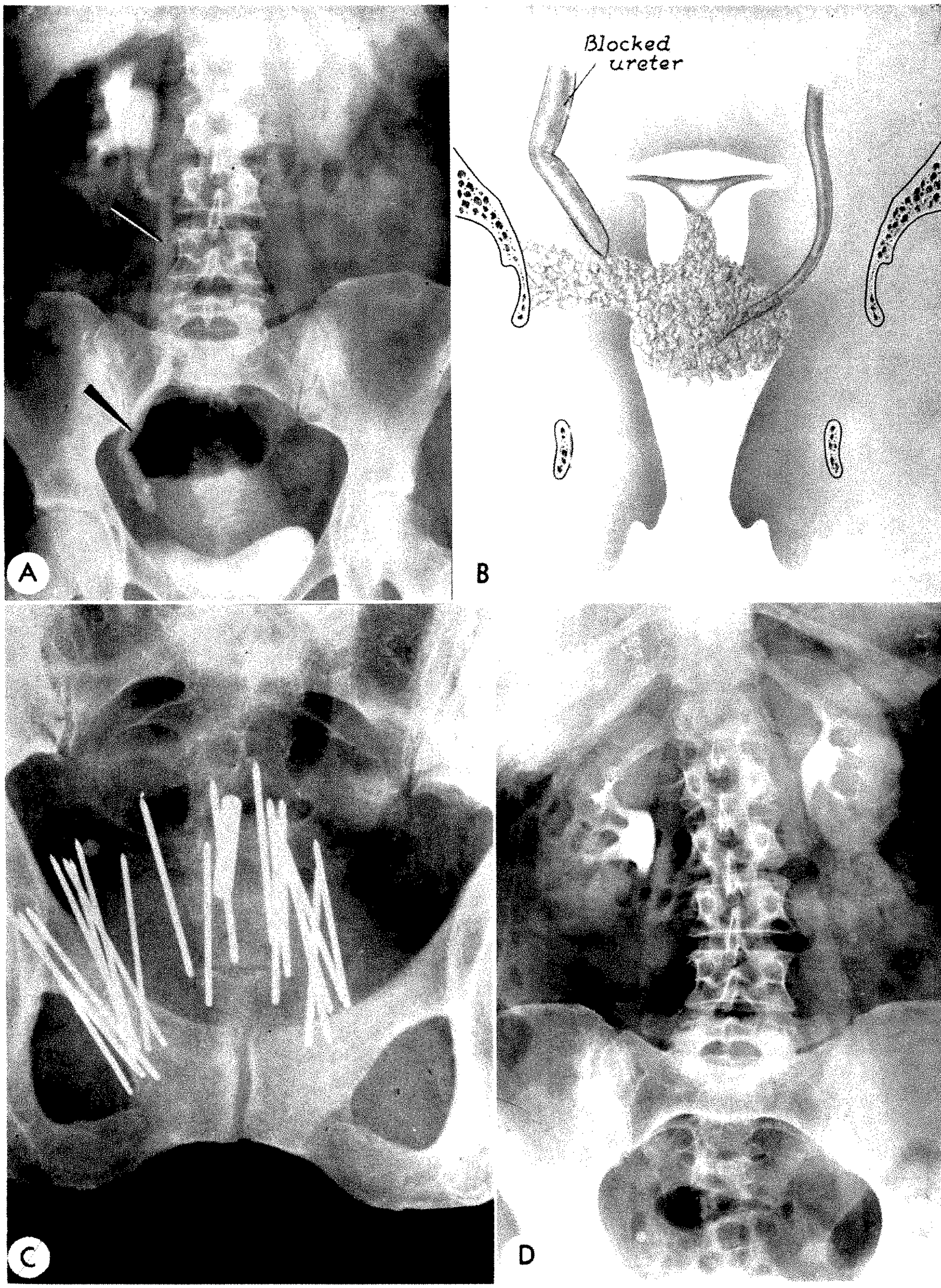

Fig. 5. Case v. Right sided hydronephrosis from malignant invasion of the parametrium (*A* and *B*) 5 months following the implantation of low intensity radium needles in the cervix and parametrium and insertion of a low intensity cervical capsule (*C*) for 7 days and the administration of conventional roentgen therapy to the right pelvis. (*D*) The urinary tract is still normal at the end of 5 years.

ureters when they are delivered as gamma rays emitted by low intensity interstitial sources. Cases are described in which ureteral strictures secondary to malignant parametrial invasion were caused to disappear by the implantation of low intensity radium needles in the parametria.

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SURVIVAL IN INVASIVE CARCINOMA OF THE CERVIX FIVE TO TEN YEARS AFTER RADIATION THERAPY*

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ALTHOUGH the recent emphasis on early diagnosis of carcinoma of the cervix is commendable, it tends to obscure the fact that even advanced lesions may respond satisfactorily to treatment. It appears to be unnecessarily pessimistic to believe that further improvement in the salvage of patients with carcinoma of the cervix is impossible by the utilization of radiation or surgical procedures; this pessimism is unwarranted because (1) these are the only successful methods of treatment available for this condition at the present time and (2) further improvement in both techniques is entirely possible. Obviously, further basic research in the biology of cancer and new avenues of treatment are essential. It also appears, however, that a more thorough study of patients already treated might yield additional information. Most of the reported series of cases of cervical carcinoma are based on five year survival; some of the surgical literature includes even shorter periods of observation. However, now that therapeutic techniques have become somewhat stabilized, it is increasingly important to examine the causes of death after treatment following a survival interval of more than five years. Such studies are particularly informative in carcinoma of the breast.

It is the practice of those responsible for the Annual Report on the Results of Treatment in Cancer of the Uterus[1] to report results at periods of five, seven and ten years after treatment. Table I shows the five and ten year survival rates from four institutions referred to in the above report that are somewhat comparable to those of the Mayo Clinic regarding the volume of patients treated. Survival rates at five years have been reported from our series, but the ten year results have not been compiled previously.

TABLE I

SURVIVAL RATES IN CARCINOMA OF THE CERVIX TREATED AT VARIOUS LOCALITIES

Locality	Patients Alive without Disease			
	Five Year Follow-up		Ten Year Follow-up	
	No.	Per Cent	No.	Per Cent
Stockholm	834	48.5	548	36.9
Manchester	665	39.4	480	29.6
St. Louis	228	55.6	60	30.3
Copenhagen	763	50.8	546	37.2

SCOPE OF PRESENT STUDY

The patients reported on here include all those treated at the Mayo Clinic from 1940 through 1949. A previous report[3] described the five year survival of patients treated from 1940 through 1948, including many of those involved in the present study. However, all cases of noninvasive carcinoma of the cervix have been excluded from the present group. Also, a careful pathologic and clinical re-evaluation of all tumors has shown that some previously considered as Stage I lesions were actually carcinoma *in situ*, and they have been deleted from the

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TABLE II

CLASSIFICATION OF 1,300 CARCINOMAS OF THE CERVIX: MAYO CLINIC, 1940–1949

Type of Lesion	Time of Treatment			
	1940–1944		1945–1949	
	No.	Per Cent	No.	Per Cent
Squamous cell epithelioma Stage I	55	8.4	78	11.9
Stage II	152	23.5	191	29.3
Stage III	207	32.1	164	25.2
Stage IV	106	16.4	52	7.7
Modified	84	13.1	121	18.5
Other carcinomas	42	6.5	48	7.4
Total	646	100.0	654	100.0

present series. Table II shows the distribution of the present series according to stages of the lesions; the patients are divided into two main subgroups, namely, those treated from 1940 through 1944, and those treated from 1945 through 1949. The first subgroup numbered 646, and the second numbered 654, giving a total of 1,300 cases. The category designated as "modified" includes all patients in whom a definitive attempt at treatment of the cervical carcinoma, whether surgical or by radiation, had been made before we saw the patient. The group called "other carcinomas" includes adenocarcinoma, adenoacanthoma and hemangio-endothelioma (1 case).

It is extremely difficult to arrive at accurate staging of the lesions in the modified group of cases, but an attempt was always made to do this for the sake of our own comparative observations.

During the decade of 1940 through 1949, a definite shift occurred in lesions of the earlier stages. In the first five year period, 32 per cent of the lesions were Stage I or II; in the latter five years, 41 per cent were in this category. The more extensive lesions changed even more dramatically; Stage III and IV lesions from 1940 through 1944 comprised 49 per cent of the total, whereas only 33 per cent were in this category during the second half. The modified group increased from 13 to 19 per cent, which reflects the changing pattern of our particular practice in that more patients are being treated prior to examination at the clinic and, consequently, the percentage of complicated problems is increasing.

TREATMENT

Table III shows the different forms and combinations of treatment utilized. Definitive radiation therapy was given to 1,143 patients. Surgical treatment alone or with postoperative irradiation was employed in the remaining 157 patients. The division

TABLE III

TREATMENT OF 1,300 CARCINOMAS OF THE CERVIX: MAYO CLINIC, 1940–1949

Type of Treatment	Time of Treatment			
	1940–1944		1945–1949	
	No.	Per Cent	No.	Per Cent
Radium alone	48	7.4	51	7.8
Roentgen rays alone	16	2.5	35	5.4
Radium and roentgen rays	508	78.6	485	74.1
Surgery alone	17	2.7	37	5.6
Surgery and radium	2	0.3	2	0.3
Surgery and roentgen rays	30	4.6	22	3.4
Surgery, radium and roentgen rays	25	3.9	22	3.4
Total	646	100.0	654	100.0

of patients according to the type of treatment remained remarkably constant in the two five year periods. In the first period, 88 per cent received radiation therapy primarily and 12 per cent received surgical treatment primarily; these percentages in the second period were 87 and 13, respectively. Thus, there was no pronounced change in philosophy regarding the management of carcinoma of the cervix throughout this decade.

Details of Therapeutic Technique. The technical details of radiation therapy at the clinic vary somewhat from those of methods used elsewhere. Our technique has been described previously,[3] but a brief recapitulation is essential to the interpretation of the tables that follow.

A complete course of treatment for carcinoma of the cervix, carried out whenever cure appears to be possible, covers a period of about four weeks. Thorough general and pelvic examinations yield essential information regarding the physical status of the patient and the stage or extent of the tumor according to the international classification. Biopsy of the growth is always performed, and its malignancy is graded according to Broders' classification. In cases of carcinoma of Stage III or IV, excretory urograms and proctoscopic examinations are made.

Treatment is started with radium; roentgen or radiocobalt (Co^{60}) therapy is instituted within one or two days and continued concurrently with the radium therapy. The unit of radium is the 50 mg. tube filtered with 1 mm. of platinum. The active length of the tube is 11.7 mm. The over-all length is 19 mm. and the diameter is 4.0 mm. Because of this small diameter, dilatation of the cervix is avoided. Trauma is minimal, and good exposure of the cervix is obtained by having the patient assume the knee-chest position at every treatment with radium; the resultant expansion of the vagina with air affords space for packing with abundant amounts of gauze after insertion of the radium tube.

Applications of radium usually are made twice weekly for a period of four weeks throughout treatment. In the absence of complications, such as infection or hemorrhage, hospitalization is necessary only on the day and night of the radium treatments. In the two or three day interval between applications of radium, the patient is ambulatory. Being out of the hospital and up and around increases the strength and morale of the patient.

In the application of radium, an effort is made to obtain homogeneous irradiation along the entire birth canal. The 50 mg., platinum-filtered tube is placed in the proximal portion of the cervical canal for ten to fourteen hours at each of the first two treatments, the posterior vaginal wall being packed well away from the radium to secure protection of the rectum. In the third and fourth treatments, also of ten to fourteen hours each, the tube is placed in the middle or deeper part of the cervical canal.

Since cervical carcinoma frequently spreads through the internal os to involve the endometrium, a tandem is introduced into the uterine cavity at the fifth radium treatment, two 50 mg. tubes being used for a period of twenty to twenty-four hours. Roentgen therapy necessarily is omitted on this day. The last three treatments are given in the vaginal cavity, the 50 mg. tube being enclosed in a plastic cylinder of appropriate size. The cylinder used most frequently has a wall that is 1 cm. in thickness; it is placed transversely across the face of the cervix, then in the right vaginal fornix, and finally in the left vaginal fornix, for a treatment time of ten to fourteen hours in each locality.

Thus, a complete course of treatment for a small lesion in a patient with a small vaginal cavity would total about 5,500 mg. hours in four weeks; a bulky carcinoma would receive a minimum of 7,300 mg. hours. Point A would receive at least 7,000 gamma roentgens and point B would receive at least 2,000 gamma roentgens in a large tumor with full dosage.

All of the patients with whom this report is concerned were treated during the period

of 1940 through 1949, and the technique of roentgen therapy in the majority of instances differed from the present scheme. Treatment was administered after completion of the course of radium therapy. Two anterior and two posterior pelvic ports were treated, each of which measured approximately 15 by 15 cm.; there was no midline separation between adjacent fields. A total dose of 540 r (air) was administered to a single field daily, employing 200 kv. with a half value layer of 1.0 mm. of copper. The course of treatment was repeated after an interval of three months.

At the present time, roentgen therapy is administered to two anterior and two posterior pelvic ports, with midline protection between adjacent zones. Daily treatments of 200 r (air) are delivered at a distance of 50 or 70 cm. to each of two ports for a total dose of 2,000 to 2,400 r per port, employing 250 kv. with a half value layer of 1.3 mm. of copper. However, many patients receive cobalt 60 teletherapy, and a midplane pelvic tumor dose of 3,500 to 3,700 r is delivered.

After treatment, the patients are examined every three months during the first year. If satisfactory healing has occurred, they are seen twice during the second year and yearly thereafter. This method of treatment relies more on radium therapy than do many other techniques. The applications of radium take care of the entire uterus, and the roentgen or cobalt 60 teletherapy is relied on to supplement the radium in an effort to sterilize any spread of carcinoma into the lateral pelvic lymph nodes.

Some patients cannot be given the entire course of radiation. The most common reasons for limiting therapy are far-advanced disease, pelvic cellulitis or pronounced debility of the patient. Other generalized diseases may require modification of the treatment. Patients in whom the entire course of therapy could not be completed are listed in the following tables under "limited radiation therapy." All others are included under "complete radiation therapy."

RESULTS

Complete Radiation Therapy (1940–1944). In the interval from 1940 through 1944, a total of 431 patients received complete radiation therapy (Table IV). The survival rate of the traced patients was 56 per cent after five years and 49 per cent after ten years. These data emphasize that extremely few Stage I lesions were treated by radiation in this interval, the majority of such lesions being treated surgically. The relatively excellent survival rate in each of the groups demonstrates the good general condition of the patients.

Limited Radiation Therapy (1940–1944). Table V indicates that 141 patients received limited radiation therapy during the first five year period. The five year survival rate was only 24 per cent, and the ten year survival rate was 19 per cent. Nearly half of the patients in this group were in the modified category, in which the rates were 23 and 13 per cent, respectively. Many of these patients obviously received benefit from further treatment, limited though it was.

Thus, from 1940 through 1944, a total of 572 patients received radiation therapy for carcinoma of the cervix, with a five year survival rate of 48 per cent and a ten year survival rate of 42 per cent.

Complete Radiation Therapy (1945–1949). A total of 403 patients received complete radiation therapy from 1945 through 1949 (Table VI). The number of Stage I lesions treated by radiation significantly increased during this second five year period as the result of two factors, namely, (1) more Stage I lesions were seen and (2) the number treated surgically decreased somewhat. The survival rate of the entire group of patients was 61 per cent for five years and 49 per cent for ten years, which is not remarkably different from the previous five year interval. The change in the number of Stage II lesions is noteworthy. A considerably larger group of patients with such lesions was seen in the latter part of the decade; a corresponding decrease in the total number of Stage III lesions occurred.

TABLE IV

SURVIVAL DATA AFTER COMPLETE RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1940–1944

Type of Lesion	Patients		Lived Five or More Years after Treatment		Patients		Lived Ten or More Years after Treatment	
	Total	Traced	No.	Per Cent*	Total	Traced	No.	Per Cent*
Squamous cell epithelioma Stage I	7	7	5	71.4	7	7	5	71.4
Stage II	137	132	105	79.5	137	132	95	72.0
Stage III	189	185	97	52.4	189	182	82	45.1
Stage IV	62	61	16	26.2	62	61	13	21.3
Modified	15	13	2	15.4	15	13	1	7.7
Other carcinomas	21	19	8	42.1	21	19	7	36.8
Total	431	417	233	55.9	431	414	203	49.0

* Based on traced patients. Inquiry as of January 1, 1960.

TABLE V

SURVIVAL DATA AFTER LIMITED RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1940–1944

Type of Lesion	Patients		Lived Five or More Years after Treatment		Patients		Lived Ten or More Years after Treatment	
	Total	Traced	No.	Per Cent*	Total	Traced	No.	Per Cent*
Squamous cell epithelioma Stage I	2	2	1	50.0	2	2	1	50.0
Stage II	8	8	6	75.0	8	8	6	75.0
Stage III	14	14	7	50.0	14	14	6	42.9
Stage IV	38	38	2	5.3	38	38	2	5.3
Modified	69	62	14	22.6	69	62	8	12.9
Other carcinomas	10	8	2	25.0	10	8	2	25.0
Total	141	132	32	24.2	141	132	25	18.9

* Based on traced patients. Inquiry as of January 1, 1960.

TABLE VI

SURVIVAL DATA AFTER COMPLETE RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1945-1949

Type of Lesion	Patients		Lived Five or More Years after Treatment		Patients		Lived Ten or More Years after Treatment	
	Total	Traced	No.	Per Cent*	Total	Traced	No.	Per Cent*
Squamous cell epithelioma Stage I	31	30	27	90.0	31	29	24	82.8
Stage II	168	164	112	68.3	168	146	85	58.2
Stage III	132	132	68	51.5	132	119	45	37.8
Stage IV	34	32	15	47.0	34	31	13	41.9
Modified	19	18	8	44.4	19	18	1	5.6
Other carcinomas	19	18	9	50.0	19	17	7	41.2
Total	403	394	239	60.7	403	360	175	48.6

* Based on traced patients. Inquiry as of January 1, 1960.

This can only be explained by the earlier recognition and treatment of the disease, since few of these patients were treated surgically in either interval.

Limited Radiation Therapy (1945-1949). A total of 168 patients received limited radiation therapy in the interval from 1945 through 1949, with five and ten year survival rates of 24 and 11 per cent, respectively (Table VII). A discouraging note with this group is the pronounced increase in the so-called modified group. This reflects the fact that more localities from which our practice derives are providing radiation therapy or attempting radical surgical procedures than formerly and that more patients who have resistant or poorly responding lesions come to the clinic for treatment. The salvage rate in these patients is necessarily far less than it is in those treated primarily.

All Types of Radiation Therapy (1940-1949). Table VIII is a composite of the four preceding tables summarizing all patients treated from 1940 through 1949. The total of 1,143 patients had five and ten year survival rates of 49 and 40 per cent, respectively. A total of 40 patients (3.5 per cent) were lost to follow-up in five years, with 79 patients (7 per cent) lost to follow-up in ten years. These therapeutic results are not too dissimilar from the figures reported by the four other medical centers shown in Table I. They indicate ample room for improvement not only by the introduction of new techniques but also by further education of the public and meticulous application of the methods now available.

Deaths. Table IX shows the number of traced patients who died between five and ten years after treatment with radiation. This excludes deaths in patients whose lesions were modified by previous treatment, who had lesions other than squamous cell epithelioma, or who did not receive the complete course of radiation therapy. The greatest number of deaths occurred in the sixth year after treatment. The great majority of deaths were in patients with Stage II or III lesions. This is to be expected, since Stage I lesions that have been controlled for five years should remain so,

TABLE VII

SURVIVAL DATA AFTER LIMITED RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1945–1949

Type of Lesion	Patients		Lived Five or More Years after Treatment		Patients		Lived Ten or More Years after Treatment	
	Total	Traced	No.	Per Cent*	Total	Traced	No.	Per Cent*
Squamous cell epithelioma Stage I	2	2	1	50.0	2	1	0	0
Stage II	12	12	7	58.3	12	11	4	36.4
Stage III	22	21	10	47.6	22	21	7	33.3
Stage IV	22	22	2	9.1	22	22	0	0
Modified	96	90	15	16.7	96	90	4	4.4
Other carcinomas	14	13	3	23.1	14	13	3	23.1
Total	168	160	38	23.8	168	158	18	11.4

* Based on traced patients. Inquiry as of January 1, 1960.

TABLE VIII

SURVIVAL DATA AFTER ALL TYPES OF RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1940–1949

Type of Lesion	Patients		Lived Five or More Years after Treatment		Patients		Lived Ten or More Years after Treatment	
	Total	Traced	No.	Per Cent*	Total	Traced	No.	Per Cent*
Squamous cell epithelioma Stage I	42	41	34	82.9	42	39	30	76.9
Stage II	325	316	230	72.8	325	297	190	64.0
Stage III	357	352	182	51.7	357	336	140	41.7
Stage IV	156	153	35	22.9	156	152	28	18.4
Modified	199	183	39	21.3	199	183	14	7.7
Other carcinomas	64	58	22	37.9	64	57	19	33.3
Total	1,143	1,103	542	49.1	1,143	1,064	421	39.6

* Based on traced patients. Inquiry as of January 1, 1960.

Table IX

NUMBER OF DEATHS* FIVE TO TEN YEARS AFTER COMPLETE RADIATION THERAPY FOR CARCINOMA OF THE CERVIX

Type of Lesion	Year after Radiation					Total
	6th	7th	8th	9th	10th	
Squamous cell epithelioma Stage I	0	0	2	0	0	2
Stage II	7	3	3	3	5	21
Stage III	9	4	4	6	3	26
Stage IV	3	2	0	2	0	7
Total	19	9	9	11	8	56

* This excludes patients whose lesions were modified by previous treatment elsewhere or who had lesions other than squamous cell epithelioma.

and the vast majority of patients with Stage IV lesions are already dead. Van Herik and Fricke[5] noted a steady decrease in the incidence of recurrence from the time of treatment to the fifth year, and this apparently occurs also in the interval from five to ten years. Table X is an attempt to classify the deaths between five and ten years on the basis of metastasis or recurrence, or the presence of other diseases. This is particularly difficult in our type of practice, because many patients come from a distance and the terminal phases are observed by the home physician. As far as can be determined, 32 of the 56 deaths during this period resulted from recurrent or metastatic carcinoma of the cervix and 8 patients died from other causes, such as a cerebrovascular accident or cardiac disease; in the remaining 16 cases, not enough information was available to allow accurate determination of the cause of death.

COMMENT

According to Miller and associates,[4] the basic concepts of the treatment of carcinoma of the cervix remain in a "polemic groove oscillating between irradiation and surgery." Our associates and we have attempted to avoid this by the team approach to a decision regarding treatment. With few exceptions, all of the patients in this series were seen and evaluated by a gynecologist, a radiation therapist and a surgeon, and then the decision was made as to the best type of treatment for the individual patient. This approach has merit but is by no means infallible, since human error cannot be so easily eliminated.

Table X

CAUSE OF DEATH* FIVE TO TEN YEARS AFTER COMPLETE RADIATION THERAPY FOR CARCINOMA OF THE CERVIX

Type of Lesion	Cause of Death			Total
	Recurrent or Metastatic Carcinoma	Disease Other Than Carcinoma of Cervix	Unknown	
Squamous cell epithelioma Stage I	1	0	1	2
Stage II	9	6	6	21
Stage III	18	2	6	26
Stage IV	4		3	7
Total	32	8	16	56

* This excludes the same patients as in Table IX.

When the results of therapy in the decade under consideration were divided into two five year intervals a significant trend could be seen in the second interval toward earlier recognition and treatment of the disease. It is hoped, and the clinical impression supports this view, that this trend has continued. At the same time, however, an increased number of patients were seen with lesions whose course had been modified by previous treatment that, in many instances, was incomplete according to the best standards. The low rate of salvage in such patients has been emphasized.

Much information is bound to be forthcoming from studies such as those recently initiated by Cosbie[2] in which the patients have been observed from the time of treatment to their death. The nature of the source of our patients makes it difficult to pursue such a program at our institution, but attempts are current to follow our treated patients more systematically than heretofore has been the rule. Determination of the five year survival rate is more important in carcinoma of the cervix than it is in many other tumors, but much valuable information will be lost if the follow-up is terminated at this point.

SUMMARY AND CONCLUSIONS

The 1,300 patients included in this report comprise all those treated for carcinoma of the cervix at the Mayo Clinic from 1940 through 1949. Definitive radiation therapy was given to 1,143 patients, and 157 patients were treated primarily by surgical techniques.

The over-all survival rate for the 1,143 patients who received definitive radiation therapy was 49 per cent for five years and 40 per cent for ten years. If all the patients lost to follow-up were considered to have died of carcinoma of the cervix, the survival rate would be 47 per cent for five years and 37 per cent for ten years.

Of the 56 patients with squamous cell epithelioma of the cervix treated primarily at the clinic who died between five and ten years after treatment, 32 died of recurrent or metastatic carcinoma of the cervix and 8 died of other diseases; not enough information was available in the remaining 16 cases to determine the cause of death.

A plea is made for long-term follow-up on all patients with carcinoma of the cervix in the hope that such retrospective studies may add to knowledge of the nature and behavior of this malignant tumor after treatment.

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ENDOMETRIAL CARCINOMA*

A THIRTEEN YEAR REVIEW

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THERE is a growing mass of evidence indicating that the incidence of carcinoma of the uterine fundus is approaching the incidence of carcinoma of the uterine cervix.[4,14,15,17,25] Better diagnostic methods, an increased awareness on the part of both patient and physician and the advancing age of the population are accepted as the explanation for this phenomenon. Since 1956, when the Oklahoma Hospitals began compiling records, 2.3 per cent of all cancer admissions have been patients with endometrial carcinoma. At this institution, fundal cancer is diagnosed as frequently as carcinoma of the urinary bladder and carcinoma of the rectum.

MATERIAL AND CLINICAL FINDINGS

Eighty-three women were treated for endometrial carcinoma in the University of Oklahoma Hospitals from March, 1945, to March, 1958, a thirteen year period. A statistical analysis of 82 of these patients is the basis of the present study. One patient has been lost to follow-up and is not included. Almost all the women were clinic patients and have been followed in the University Clinic's outpatient department. There were only 7 private patients and they were traced without difficulty by contacting the referring physician. The five year salvage rate is based on 50 patients treated prior to March, 1955.

Pertinent vital statistics of the 82 patients are summarized in Table I. Seventy-three were married; 22 were childless. The association of corpus cancer with sterility has been established for many years.[25,30] The significance of this relative increase with childlessness is not as yet fully understood. The average age of the patients was fifty-eight years. It is interesting to note that 84 per cent of our cases occurred after the age of fifty. The youngest woman was thirty-two, the oldest eighty-six. Of the group, 78 per cent were postmenopausal. The predisposition of this malignancy for women whose menses have ceased has been repeatedly stressed in the literature.[1,9,24,29]

Figure 1 indicates the grave significance of postmenopausal bleeding. In our series, the complaints ranged from seemingly innocuous intermenstrual spotting to sudden onset of vaginal hemorrhage many years after cessation of menses. It is apparent that postmenopausal bleeding, however slight, must be considered a manifestation of gynecologic cancer until proved otherwise by means of diagnostic dilatation and curettage. The only other symptom described with any degree of regularity was abdominal discomfort of varying nature.

For many years there has been an attempt to correlate endocrine abnormalities with the development of adenocarcinoma of the uterus.[2,6,9,17,33,34] The interrelationship of endometrial hyperplasia, hyperestrogenism and aberration of carbohydrate metabolism has been investigated extensively in the British literature.[19,30] These studies have demonstrated an abnormal incidence of benign glandular hyperplasia in patients with frank diabetes and patients with high glucose tolerance curves who are not clinically diabetic. By inference, a qualitative and quantitative relationship is assumed between hyperactivity of the anterior pituitary gland and corpus cancer. In 1935, Stein and Leventhal[31] described the syndrome which bears their name and noted that such cases were more prone to develop endometrial carcinoma than could be explained on the basis of chance. They surmised that some abnormality of the pituitary-adrenal-ovarian balance was responsible.

The endocrinopathies observed in our series are summarized in Table II: 57 were

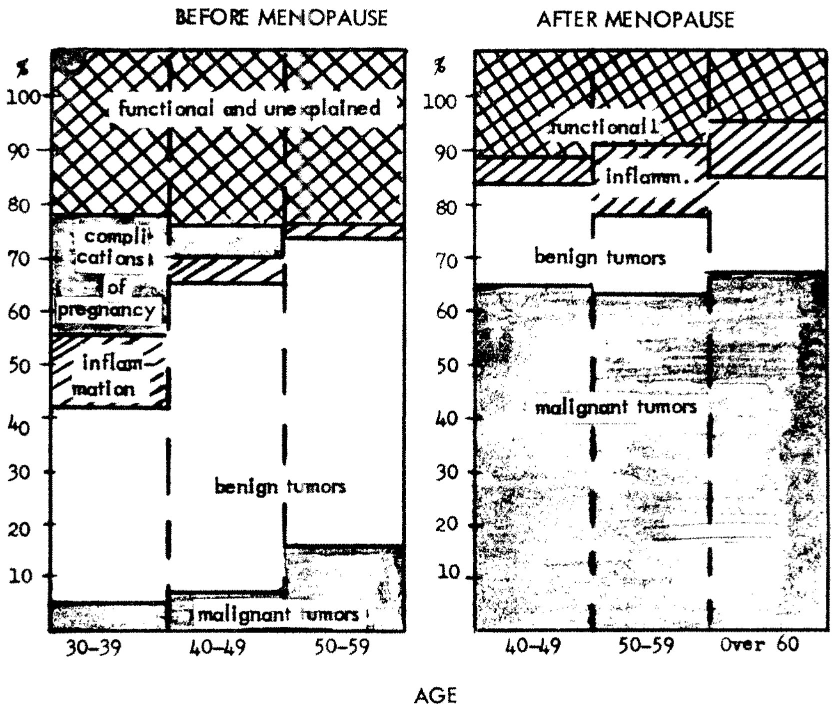

FIG. 1. Relative frequency of causes of gynecologic bleeding. Graphic evidence of the serious implication of vaginal bleeding in the postmenopausal patient. (Modified from Taylor and Millen.[34])

described as obese; 24 menstruated beyond the age of 50; 36 were definitely hypertensive with diastolic pressures of at least 100; and 13 had a clinical diagnosis of diabetes. It is noted that 12 patients presented the triad of diabetes, hypertension and obesity.

TABLE I

VITAL STATISTICS OF 82 PATIENTS WITH ENDOMETRIAL CANCER

Marital Status	90% married
Age	Range from 32–86 66% from 50–65 Average age 58
Parity	24% childless
Race	83% white
Economic Status	90% charity
Menopause	78% postmenopausal Average age at menopause 47
Symptoms	Vaginal bleeding 98% Abdominal pain 33%

In this series, the staging system set forth in the Stockholm League of Nations report[32] has been used. Stage I refers to cancer clinically confined to the uterus. Stage II includes cancer which has spread beyond the confines of the uterus, based on palpation of an irregular extrauterine mass, obvious invasion of surrounding tissue, and/or evident metastases. Of our patients,

TABLE II

ENDOCRINOPATHIES OBSERVED IN 82 PATIENTS WITH ENDOMETRIAL CANCER

Abnormality	No. of Cases	Per Cent	Per Cent of General Population
Obesity	57	70	40
Menopause after Age 50	24	40	8–15
Nulliparity	20	24	15–16
Hypertension	36	44	25–30
Diabetes	13	16	1
Ovarian Neoplasm	2	2.4	—
Hypertension, Diabetes and Obesity	12	14.6	—

77 per cent were classified as Stage I; 23 per cent as Stage II. Unavoidable errors in classification are inherent in this staging system, since clinical criteria alone are utilized. In retrospect, it can be assumed that most of the Stage I patients who died of progressive disease were undetected Stage II cases at the time of treatment.

Histologic diagnoses are available in all cases. Adenocarcinoma was reported in 78 patients and adenoacanthoma in 4. No attempt has been made to classify the neoplasms according to histologic grade.

TREATMENT

During the thirteen years covered by this study, several modes of therapy have been used. No fixed plan of treatment has evolved. Of the 82 cases, 36 were treated by surgery plus some form of irradiation; 29 patients underwent hysterectomy alone, receiving no other definitive therapy; and 17 were treated by irradiation alone.

In respect to comparison of modalities, the number of cases is too small and is so affected by selection that no statistically valid conclusions can be drawn. From the data available, however, some generalizations can be made. Apparently, individual selection has resulted in the use of surgery, either alone or in conjunction with irradiation, in good risk, Stage I patients. Irradiation alone has been used primarily to palliate poor risk, debilitated patients. Contraindications to surgery have included far advanced local malignancy, extreme obesity, metastatic cancer and systemic cardiovascular disease.

An evaluation of the type of radiation therapy which was administered is important. Most of the patients who were not surgical candidates were treated by a single radium application. A metal tandem containing 50–75 mg. of radium was inserted into the endometrial cavity and allowed to remain for 3,000–5,000 mg. hours. Occasionally, vaginal colpostats were utilized as an adjunct. The radium application was not followed by external roentgen therapy unless persistent or recurrent disease necessitated further treatment. When intrauterine radium was impracticable, the patient was treated by orthovoltage external roentgen therapy. The dosage varied, usually two anterior and two posterior fields were carried to skin tolerance. This approach to radiation therapy bears little relationship to the thorough, painstaking therapeutic program described by Heyman.[12,13] Therefore, it can be assumed that no patient received what is now accepted as a full course of irradiation. It is surprising and gratifying that some of the Stage I patients who were considered poor surgical candidates have been salvaged by irradiation alone.

It is interesting to note that the radium technique and dosage were essentially the same whether or not the irradiation was to be followed by surgery. Of the 36 patients who were treated by a combined approach, 27 received preoperative radium therapy delivered by tandem or needles. Nine women had far advanced local cancer, which precluded a radium application; therefore, external therapy was given prior to surgery.

RESULTS

The results of treatment according to the type of therapy and stage of the disease are shown in Table III. Apparent cures include patients who are alive and well at least two years following treatment and those who have died of intercurrent disease unrelated to uterine cancer. Thus, 61 of the 82 patients (74.4 per cent) represent apparent cures. Since 5 patients have died of unrelated causes, the absolute cure rate, then, is 56 of 82 (68.3 per cent).

Fifty patients have been followed at least five years. Twenty-nine are living and well, an absolute salvage of 58 per cent. Since 4 of these patients have died of intercurrent disease, the apparent five year survival rate is 67 per cent. Results of treatment elsewhere are summarized in Table IV.

As indicated in Table III, the major factor in ultimate prognosis is the stage of the disease at the time of diagnosis and

TABLE III

RESULTS OF TREATMENT IN 82 PATIENTS WITH ENDOMETRIAL CANCER ACCORDING TO STAGE OF THE DISEASE AND TYPE OF THERAPY

Type of Therapy	Stage I			Stage II		
	Total No. of Cases	Apparent Cures No. of Cases	Apparent Cures Per Cent	Total No. of Cases	Apparent Cures No. of Cases	Apparent Cures Per Cent
Surgery Alone	27	27	100	2	1	50
Irradiation Plus Surgery	28	26	95	8	3	38
Radium Alone*	4	2	50	2	0	—
Roentgen Rays Alone*	4	2	50	7	0	—
Total	63	57	90.5	19	4	21

* Incomplete course of irradiation by present day standards; not suitable patients for surgery.

treatment. Gratifying results can be expected in patients with cancer clinically confined to the uterus. Of the 55 Stage I cases receiving definitive treatment, only 2 are classified as treatment failures. It is significant that 4 of the 8 Stage I patients not considered surgical candidates and treated by less than optimal irradiation are living without cancer at this time.

Patients with Stage II lesions have a poor prognosis. In this series, only 3 of 19 patients have survived. One patient died in congestive heart failure four years after treatment and 15 must be classified as treatment failures. Similarly discouraging results have been reported from other institutions; the usual salvage rate in Stage II patients averages 15–20 per cent.[14,22]

TABLE IV

SUMMARY OF REPORTED RESULTS

Treatment	No. of Cases	Five Year Survival (per cent)
Preoperative Irradiation		
Heyman[12,13]	65	78
Rhode Island Hospital[3]	67	61
Hundley *et al.*[14]	81	84
Radium Alone		
Heyman[12,13]	459	62
Rhode Island Hospital[3]	28	43
Corscaden[3]	27	48
Hysterectomy Alone		
Rhode Island Hospital[3]	22	68
Arneson[1]	18	84
Masson[3]	306	67
Finn[8]	39	70

DISCUSSION

The literature on the treatment of endometrial carcinoma is quite voluminous. General surgeons, radiologists, gynecologists, and other members of the medical profession have expressed their individual and collective views for many years. As yet, no unanimity of opinion is available. Certain premises are generally accepted:

1. The diagnosis should be established histopathologically prior to any treatment.
2. The best results are obtained when a hysterectomy is practicable.
3. The results are considerably improved by judicious radiation therapy, preferably preoperative.
4. A coordinated approach utilizing the resources of the gynecologist and the radiologist is necessary, and it must include diagnosis, treatment, and follow-up care.

The superiority of a combined therapeutic approach is not universally accepted. Heyman,[13] who has had as much experience with corpus cancer as any physician in the world, believes that radiation therapy should be the primary treatment and surgery is to be performed only if uncontrolled disease persists. Conversely, some authorities[28,30] advocate immediate hysterectomy to be followed by radiation therapy in cases

Table V

COMPARISON OF REPORTED FIVE YEAR SURVIVAL RATES FOR ENDOMETRIAL CANCER TREATED BY SURGERY ALONE AND BY IRRADIATION FOLLOWED BY SURGERY

Author	Surgery (per cent)	Irradiation Followed by Hysterectomy (per cent)
Arneson[1]	79	87
Cosbie *et al.*[5]	73	85
Payne[23]	80	93
Randall, Mirick, and Wieben[26]	62	82
Randall and Goddard[25]	60	76
Schmitz *et al.*[29]	79	90

of recurrent cancer.

Intrauterine placement of radium provides an effective control of the primary neoplasm and also delivers significant dosage to the parametrial tissues and the vaginal vault. An increased incidence of recurrence in the vaginal cuff is a major disadvantage of the use of surgery alone.[15,17] Several investigators have published salvage rates for surgery as compared to their results with combined irradiation and surgery (Table v). As a result of their studies, they have become champions of combined treatment.[4,5,14,16,22,23,26] Optimum preoperative radium treatment eradicates histologic evidence of cancer in 60–90 per cent of operative specimens.[1,10,15,28] In our series, no malignant cells were identified in 71 per cent of the uteri which had been treated by radium prior to surgery.

Most authorities recommend that surgery follow irradiation within four to six weeks if at all possible.[14,34] Primary radiation therapy without subsequent surgery is advised only in cases made inoperable by nonresectability, severe systemic disease, and refusal of the patient to undergo the operation.

At the present time, most therapists utilize a technique whereby the uterine cavity is packed with multiple small sources of radium.[3,15,17,33,34] This procedure delivers a relatively homogeneous dosage of irradiation to all segments of the endometrium. Additional radium in the vaginal vault is aimed at preventing recurrence in this region. (Only 1 patient in this series was treated by the multiple capsule method, but during the past two years this technique has been used more frequently.) In some centers, supervoltage roentgen therapy has proved effective, especially in inoperable patients with extensive pelvic disease which precludes radium application.

SUMMARY

Eighty-two patients treated for endometrial carcinoma at the University of Oklahoma Hospitals from 1945–1958 are reviewed. All of the patients have been followed for at least two years and 50 of these comprise the five year group. Fifty-six patients are living and well (68.3 per cent). The absolute survival rate in the patients followed five or more years is 58 per cent.

The grave significance of postmenopausal vaginal bleeding is emphasized. A diagnostic dilatation and curettage is imperative in all women who present with this complaint. The index of suspicion should be especially high in patients with various endocrinopathies, such as those evidenced by hypertension, benign endometrial hyperplasia, obesity, and diabetes.

The most important factor in ultimate survival is the stage of the disease at the time of diagnosis and treatment. The prognosis is excellent in cases in which the cancer is still clinically confined to the uterus.

When endometrial carcinoma is present, the treatment of choice is preoperative radium application followed by complete abdominal hysterectomy.

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INCIDENCE OF PELVIC MALIGNANCIES FOLLOWING IRRADIATION FOR BENIGN GYNECOLOGIC CONDITIONS*

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CRITICAL reviews of the late results of the use of radiation therapy in benign conditions are in order because of the variable incidence of subsequent carcinogenesis reported by many authors. Procedures once considered routine, such as thymic irradiation of children with widened mediastinal shadows and spinal irradiation of adult males with rheumatoid spondylitis, have been largely abandoned in the past decade. The value of any form of therapy depends upon its success initially and its complications and death rate subsequently. It is generally agreed that any significant development of malignancy must be carefully weighed when radiation therapy is considered for benign lesions.

The incidence of pelvic malignancies following the use of radium and external irradiation in benign gynecologic conditions has been intensively reported in the gynecologic literature with virtual exclusion in radiologic journals. Until 1956, no report presented unequivocal evidence that irradiation for benign uterine bleeding predisposed to the subsequent development of pelvic neoplasia. Palmer and Spratt[15] found a 6.6 per cent incidence of late genital cancers in their series at Roswell Park Memorial Hospital, higher than that reported by any other author, and stated that "previous irradiation is, at least in part, responsible for subsequent malignancy." As these authors have noted, there are numerous pitfalls which may invalidate such a study. Before evaluating the different facets of the present survey, a review of the literature is in order to help define the issues more clearly.

REVIEW OF THE LITERATURE

Previous studies exploring the problem of cancer induction following pelvic irradiation for gynecologic diseases of a benign nature have been along two lines: (1) the prospective approach, in which patients irradiated for benign bleeding have been followed for various periods to determine what percentage developed pelvic cancers; and (2) the retrospective approach in which patients with gynecologic cancers have been studied to determine the percentage previously irradiated for benign lesions.

As early as 1925, Werner[22] noted an incidence of 0.3 per cent of gynecologic cancer in 2,680 patients subsequent to radiation therapy for menstrual disorders. A year later, in 1926, Vogt[21] substantiated this finding with a 0.4 per cent occurrence rate of endometrial carcinoma in 1,300 patients treated by radiation as opposed to a 5 per cent incidence of fundal carcinoma in all patients with menopausal bleeding. He concluded that radium therapy was protective in that the rate of malignancy was decreased by a factor of ten.

A case report of endometrial carcinoma seven years following roentgen-ray induced menopause was recorded by Macfarlane[10] in 1932 with a review of the literature to 1915. A total of 29 cases in seven articles, all in the German literature, was analyzed. The author concluded, "it is evident that the possibility of developing carcinoma in the uterus after radiation is very remote."

In 1934, Schmitz[18] found only 1 case of malignancy in 578 patients treated by ir-

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Table I

REVIEW OF THE LITERATURE

Author	Year	No. of Cases	Cases Followed		Interval (yr.)	Gynecologic Malignancies	
			No.	Per Cent		No.	Per Cent
Schmitz[18]	1934	578	578	100	6 (av.)	1	0.17
Costolow[2]	1941	1,009	986	98	2.5–12.5	4	0.40
Corscaden *et al.*[1]	1946	1,100	958	88	6.7 (av.)	17	1.90
Crossen and Crossen[3]	1947	526	526	100	5 (av.)	5	0.95
Montgomery *et al.*[12]	1952	1,232	831	69	0.5–21	12	1.40
Hunter *et al.*[8]	1954	765	644	84	5 –20	3	0.50
Palmer and Spratt[15]	1956	1,670	721	43	10 –20	51	6.60
Stander[19]	1957	964	735	76.5	10 –24	19	2.60
Rubin *et al.*	1960	489	310	64	5 –33	7	2.20

radiation for benign uterine lesious (Table 1) and he questioned the role of radium in the cited case since atypia had been noted in the histologic sections eighteen months earlier. Later in the thirties, isolated instances of 1 or 2 cases of malignancy after irradiation of the uterus were described by Strachan,[20] Malpas,[11] Essen-Moller, and Luker[9] in the British literature.

In the forties, a number of larger series was reported (Table 1). In 1941, Costolow,[2] analyzing 1,009 cases of uterine fibroids treated by radium, found 4 cases of malignancy for an incidence of 0.4 per cent. Scheffey[17] a year later added 20 cases to the 71 so far reported of malignancy subsequent to irradiation of the uterus for benign conditions. Although he is often referred to as the first author implicating irradiation as a cause of the cancer, he concludes his paper with a statement of the opposite point of view, "errors of omission, either in technique or in judgment . . . not the radiation therapy itself, were the responsible factors in the subsequent occurrence of malignancy."

Corscaden *et al.*[1] in 1946 carefully reviewed their series and found 22 cases of pelvic neoplasia of which 18 were gynecologic in origin, representing a 1.9 per cent incidence rate. They expressed the opinion that the abnormal bleeding rather than irradiation was responsible for the malignancies. Crossen and Crossen[3] in the *only* controlled study showed that irradiation of uterine fibroids reduced the incidence of ovarian cancer and endometrial carcinoma. Thus, in 2,136 cases of nonirradiated myomas there were 13 cases of ovarian cancer (0.68 per cent) and 37 cases of fundal cancer (1.7 per cent) as opposed to an incidence in 526 cases of irradiated myomas of 1 case (0.19 per cent) of ovarian cancer and 4 cases (0.7 per cent) of fundal cancer.

In 1952, Montgomery *et al.*[12] found 12 cases of pelvic cancer in 831 cases of benign uterine bleeding treated by radium. Comparing the mortality and morbidity of surgery with the 1.4 per cent incidence of malignancy after utilization of radiation techniques, they concluded that the risk of radium therapy is very small and is to be preferred. Healy, in discussing this report, also felt that no relationship between irradiation and the late development of uterine carcinoma and sarcoma existed. Hunter *et al.*,[8] in 1954, presented a critical twenty year survey of their experience in the use of radium for the treatment of benign uterine lesions. After finding 3 late cases of gynecologic malignancies in 644 patients, they concluded, "an alleged high incidence of post-irradiation malignancy . . . has never been demonstrated by an analysis of actual clinical experience."

In 1956, Palmer and Spratt[15] sent questionaires to 1,670 patients treated with radium and roentgen rays for benign

uterine abnormalities. As mentioned, they found an unusually high incidence (6.6 per cent) of late malignancies compared to other authors. This they felt was due to the long follow-up (more than ten years) in their study; however, no mention was made of the fact that they had one of the lowest response rates in the literature with only 43 per cent of the patients answering and the consequent deletion of more than half of their series.

A comparable but much more complete experience was offered by Stander[19] in 1957 from the University of Michigan. In a study encompassing 964 patients who had radiation castration, 735 (76.5 per cent) were traced from ten to twenty-four years (average 16.6 years). There were 19 gynecologic cancers found for an incidence of 2.6 per cent, with endometrial carcinoma being the major group (14 cases). The author felt that the irradiation was not carcinogenic in pelvic structures and that the increased occurrence of endometrial carcinoma was due to endocrine abnormalities. Since the same control group was used in this series as in the Palmer and Spratt report,[15] one readily observes the conflicting and confusing nature of this survey of the literature.

MATERIAL

BENIGN GYNECOLOGIC CONDITIONS IRRADIATED

From 1927 to 1958, there were 469 cases of benign gynecologic conditions in our series which were irradiated by means of roentgen rays and radium. In Table II, the various disorders are listed. The majority of the lesions treated (68.2 per cent) were in those patients presenting with profuse and irregular menopausal and postmenopausal vaginal bleeding. Endometrial hyperplasia, histologically proved, constituted the largest single group, or 60 per cent, of the series. Curiously, myomata comprised only 13 per cent. Other reasons for irradiation such as endometriosis, sterilization, infections and infertility accounted for a relatively small percentage of the series. Beneficial results occurred in

Table II

BENIGN GYNECOLOGIC CONDITIONS IRRADIATED 1927–1958 (469 CASES)

	No. of Cases	Per Cent
Endometrial Hyperplasia (histologically proved)	287	60
Excessive Uterine Bleeding (histologically normal)	86	17
Myomata Uteri	48	13
Endometriosis	16	3
Cervicitis	9	1.8
Sterilization for Various Reasons (anemia, psychiatric conditions)	9	1.8
Excessive Uterine Bleeding (no histology)	6	1.2
Infections	4	0.8
Infertility	2	0.4
Pruritus Vulvae	2	0.4

more than 90 per cent of these cases, as has been noted in similar instances by many authors.[1,12]

In reviewing the distribution of cases (Fig. 1), it was found that radium insertion for endometrial hyperplasia was done most frequently from 1940 to 1949. In the past decade, there has been a gradual supplanting of radiation therapy with hormonal regimes and surgical methods, either curettage alone or, if indicated, hysterectomy. In the last few years, sterilization for medical or psychiatric reasons has been done by irradiation only when surgery was contraindicated.

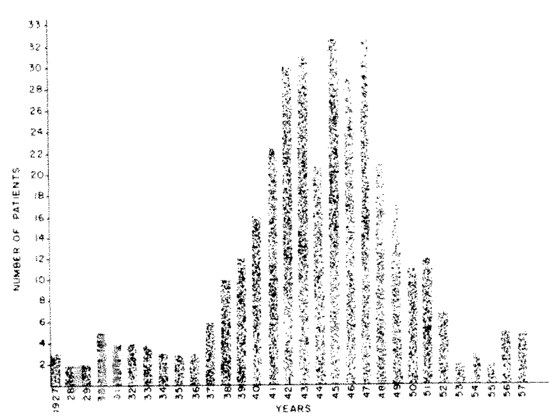

Fig. 1. Number of patients with benign gynecologic conditions treated each year.

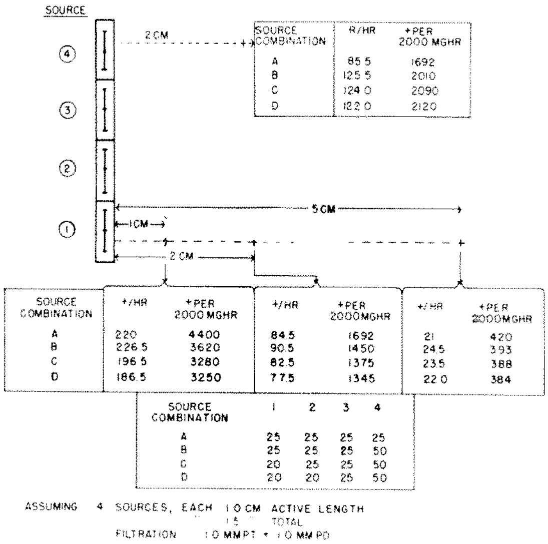

FIG. 2. Radium distribution and dosage in benign gynecologic lesions; assuming 4 sources, each of 1.0 cm. active length, and 1.5 cm. total length. Filtration: 1.0 mm. Pt and 1.0 mm. Pb.

AGE DISTRIBUTION

The main group of our patients was either menopausal or postmenopausal. The age bracket between forty and fifty-five years contained 82 per cent of our series. Only 14 per cent were below the age of forty and 4 per cent were past the fifty-five year mark.

IRRADIATION TECHNIQUES

1. *Intrauterine Radium.* In 75 per cent of our cases, 359 patients, a radium stem was placed in the uterine canal. This consisted of a varying number of sources (1–5) filtered with 1.0 mm. Pt and 1.0 mm. Pb depending upon the length of the canal. The total amount of radium varied from 50 to 100 mg. and this was left in place from 24 to 50 hours. The average application was 2,400 mg. hr. ±400 mg. hr. The estimated dose in the pelvis to point A was 2,000 r (maximum) and to point B was 500 r (maximum). For a detailed analysis of treatment factors see Figure 2.

2. *External Irradiation.* A smaller group of 130 cases, or 25 per cent of our series, received external irradiation with the following factors: 220 kv., half value layer 1.0 mm. Cu, 2 opposing 15×15 cm. ports; the total dose to each port was 500–1,000 r, usually fractionally delivered in two weeks; the calculated midpelvic depth dose was 500–1,000 r (average 700 r).

Name:
Address:

1. Good response to x-ray or radium treatment was:
   Permanent ______
   Temporary ______
   None ______

2. Did menstrual bleeding recur? Yes ______
   No ______

3. If yes, was further x-ray therapy or surgery required?
   Yes ______
   No ______

4. If yes, name Hospital ______
   Physician ______
   Address ______
   Date ______

5. Present Health ______

6. Any other serious illnesses or operations? ______
   If yes, was hospitalization required? ______
   Name hospital, physician and date ______

7. Other remarks:

FIG. 3. Questionnaire sent to patients.

FOLLOW-UP METHOD

A regular form letter indicating our interest in evaluating the results of treatment was sent to all patients. The questionnaire consisted of seven carefully worded statements which were nonspecific in nature (Fig. 3). Of the 469 patients, 64 per cent responded, 25 per cent never received the letter and 11 per cent failed to return the questionnaire. Repeat questionnaires were sent to the latter two groups, personal investigations and telephone calls were made when feasible and letters to physicians, health department, etc. were mailed when indicated.

CASES OF PELVIC MALIGNANCIES

The total number of cases of malignancy in our series following irradiation for benign uterine conditions came to 16 (Table III). Of these, 12 were pelvic and 4 were extrapelvic in location. Seven of the 12 were in gynecologic areas and the other 5 were in surrounding pelvic viscera. Brief case summaries (Table IV) of these pelvic malignancies are as follows.

CARCINOMA OF ENDOMETRIUM (3 CASES)

Case I. H.M., 165310, a forty-six year old female, was treated for menorrhagia with a 2,200 mg. hr. uterine stem radium application. Eight years later, a diagnosis of adenocarcinoma of the uterus was made which was treated preoperatively by Heyman's radium capsules followed by hysterectomy.

Case II. F.K., 69980, was a forty-three year old female with a history of menorrhagia shown to be due to endometrial hyperplasia following curettage. The application of a radium stem for 998 mg. hr. in 1942 was followed in 1949 by external roentgen irradiation calculated to deliver a depth dose of 720 r to the ovaries. Eight years later, recurrent menstrual bleeding was shown to be due to endometrial carcinoma which was treated preoperatively by Heyman's capsules followed by hysterectomy. Two and one half years later, she died of extensive metastases.

Case III. M.E., 13243, a forty-three year old female, was treated in 1935 for menorrhagia secondary to a myomatous uterus. A six point arrangement crossfiring the pelvis with roentgen irradiation was utilized with exposure factors recorded as 300 ma. min. Five years later a diagnosis of adenocarcinoma of the uterus was made. The patient followed a remarkable course, surviving for nineteen years with metastatic tumor the last ten years of life.

Table III

COMPARISON OF OBSERVED AND EXPECTED CANCER INCIDENCE IN THE PRESENT SERIES

Site	Observed		Expected		Probability	
Genital						
Corpus	3		1.6		0.22	
Cervix	1		1.8		0.83	
Ovary	3		0.9		0.06	
Vagina	0		0.05		1.00	
Vulva	0		0.1		1.00	
Total Genital		7		4.7		0.19
Pelvic						
Bladder	0		0.3		1.00	
Colon	4		1.6		0.08	
Rectum	0		0.6		1.00	
Anus	1		—		—	
Total Pelvic		5		2.5		0.11
Total Genital and Pelvic		12		7.2		0.06
Breast	4		4.4		0.64	
Total, All Sites (including 2 cases of cancer of the skin)		18		17.6		0.49

CARCINOMA OF CERVIX (1 CASE)

Case IV. M.M., 195337, a forty year old patient, was treated for endometrial hyperplasia by means of a radium stem containing 115 mg. for 17 hr., totaling 2,000 mg. hr. Fifteen years later, carcinoma of the cervix was detected and death followed within a year's time.

CARCINOMA OF OVARY (3 CASES)

Case V. A.V., 144816, at the age of forty-nine had a bout of menorrhagia which led to the diagnosis of endometrial hyperplasia. Treatment was with insertion of 80 mg. of radium for 31 hr., or 2,480 mg. hr. Eight years later, at laparotomy, an extensive inoperable ovarian carcinoma was found and the patient died two months later.

Case VI. F.B., 132508, a fifty-two year old female with menorrhagia but normal endometrium, following curettage received 2,500 mg. hr. of radium (100 mg. for 25 hr.). She died shortly after the diagnosis of ovarian carcinoma at laparotomy eight years later.

Case VII. P.B., 145917, a forty-eight year old female presenting with menorrhagia but histologically normal endometrium, was treated by means of an 80 mg. radium tandem for 30 hr. (2,400 mg. hr.). A diagnosis of cystadenocarcinoma of the ovary was made thirteen years later. Therapy consisted of surgery, postoperative external irradiation and isotopic instillation. The patient is alive and well without disease for two years.

CARCINOMA OF COLON (5 CASES)

Case VIII. E.O'B., 58045, a fifty-five year old female with a history of menorrhagia, was treated by a radium application. She developed a sigmoid carcinoma two months later. Without much question this could not be related to the irradiation and is therefore excluded from our series.

Case IX. M.K., 206230, at the age of forty-five, developed a vesicovaginal fistula as the

TABLE IV

PELVIC MALIGNANCIES FOLLOWING IRRADIATION OF BENIGN LESIONS

Case	Age	Indication for Treatment	Type of Treatment	Interval (yr.)	Late Cancer	Survival† (yr.)
I. H.M. 165310	46	Menorrhagia	Radium	8	Endometrial	1
II. F.K. 69980	43	Endometrial hyperplasia	Roentgen and radium	8	Endometrial	2.5
III. M.E. 13243	43	Myomatous uterus	Roentgen	5	Endometrial	19
IV. M.M. 195337	40	Endometrial hyperplasia	Radium	15	Cervical	1
V. A.V. 144816	49	Endometrial hyperplasia	Radium	8	Ovarian	8
VI. F.B. 132508	52	Menorrhagia	Radium	8	Ovarian	1
VII. P.B. 145917	48	Menorrhagia	Radium	13	Ovarian	2
VIII. E.O'B. 58045*	55	Menorrhagia	Radium	2 mo.	Sigmoid	4
IX. M.K. 206230	45	Endometrial hyperplasia	Radium	4	Colon, ascending	1
X. R.G. 297450	50	Endometrial hyperplasia	Roentgen	5	Sigmoid	1
XI. G.T. 345874	51	Endometrial hyperplasia	Roentgen	6	Cecum	2
XII. M.S. 30679	42	Endometrial hyperplasia	Roentgen	12	Sigmoid	1
XIII. M.J. 208479	50	Endometrial hyperplasia	Radium	11	Anus	5

* This case has been excluded from the series because the two month interval is too short for the carcinogenesis to be related to the irradiation.

† Still living.

result of repair of a cystocele. She also had menorrhagia and dilatation and curettage showed endometrial hyperplasia. She was treated with radium 70 mg. for 34 hr. totaling 2,380 mg. hr. Adenocarcinoma of the ascending colon was diagnosed four years after radium treatment and she died a year later of her disease.

CASE X. G.R., 297450, at the age of fifty developed menorrhagia and histologically proved endometrial hyperplasia. The following roentgen treatment factors were used: 220 kv., 15×15 cm. port anterior and posterior, and an ovarian dose of 480 r. The patient developed carcinoma of the sigmoid five years after irradiation. Resection of the sigmoid with ileocolostomy followed and she died shortly afterwards.

CASE XI. G.T., 345874, a fifty-one year old female, presented with vaginal bleeding due to endometrial hyperplasia with areas of atypia. Therapy was by means of external roentgen irradiation, 220 kv., half value layer 1.0 mm. Cu, 15×15 cm. anterior and posterior opposed pelvic fields. A depth dose of 1,714 r was delivered to the midpelvis. Six years later, a cecal carcinoma was found and resected. At death two years later, the disease had metastasized widely.

CASE XII. M.S., 30679, at the age of forty-two had metrorrhagia caused by histologically diagnosed endometrial hyperplasia. She was treated with 220 kv. roentgen rays with 15×15 cm. opposing ports, the anterior and posterior pelvis receiving a total dose of 684 r to each ovary. Twelve years later, at laparotomy, carcinoma of the sigmoid with metastases to ovaries and peritoneum was found.

CARCINOMA OF ANUS (1 CASE)

CASE XIII. M.J., 208479, at the age of fifty developed metrorrhagia which was diagnosed histologically as endometrial hyperplasia. She was treated with radium 100 mg. for 24 hr., a total of 2,400 mg. hr. Eleven years later, she developed carcinoma of the anus which was treated by surgery and irradiation.

COMMENT

Reviewing these cases of diverse tumors, one notes no correlation between their incidence and the age of the patient or the type of radiation employed. The ratio of radium applications to external roentgen treatments reflects the group distribution. The time interval before the onset of late cancer ranged from 4 to 15 years with the average being 8.7 years. It is of some inter-

est that the colon was the most frequent site of involvement.

STATISTICAL METHODS AND RESULTS

The expected and observed incidence of cancer at various sites is given in Table III. The expected values are determined by the method devised by Corscaden *et al.*[1] in which the total person-years of exposure to risk at each age is calculated, and available tables of site and age-specific *incidence rates* are applied to calculate the expected number of cases at each of the sites. The incidence rates used are those released by the Bureau of Cancer Control of the State of New York, Department of Health, for the years 1949–1951, and, in addition, the table released for the year 1958. The table for 1958 is in abbreviated form and lists specifically only major sites. Wherever possible, the rates for 1949–1951 were averaged with those for 1958 to obtain the actual incidence rates used. For minor sites, *e.g.*, vulva, only the 1949–1951 rates were used. In no case did the rates differ much from those of the 1949–1951 table.

The use of any "control" or "normal" rate table is open to strong criticism. In the discussion it will be indicated that any group presented, as ours was, for treatment of benign gynecologic bleeding is, in fact, a special group. The only adequate control group would be a matched, similarly presented group which would *not* be treated by irradiation methods. It must be emphasized that we do not use the above indicated tables unreservedly. They are tables obtained from *reported* cases (cancer has been reportable by law in New York State since 1940), including those reported on death certificates. They are for all of New York State, exclusive of New York City. They are based, at least partially, on population estimates. The same tables were used by Palmer and Spratt[15] and by Stander.[19]

A third column is included in Table III in which we have calculated the probability of at least as many incidents as were observed by us with the indicated expected values. It is notable that, although the number of cases is high for the ovary and for the colon, the over-all number of genital cases is not exceptionally high—nor is the over-all number of pelvic cancers. Compounded still further, however, the total number of pelvic region cases (12) is probably high and has a probability of only about 1 in 20 of occurring in groups of this size.

It should also be noted that the total incidence observed for cancer of all sites (including skin cancer) is 18, whereas the expected number using control rates is 17.6—almost identical!

It is our feeling that these probability figures are useful in deciding whether or not there is really an increased incidence at a particular site or combination of sites. The calculation of an observed-expected ratio is grossly misleading and inaccurate. It is misleading because it *assumes* that there is a real increase in incidence. It is inaccurate because it fails to take into account chance deviations. Considerably smaller rate increases than those expressed by the ratio could account for the observed incidence.

If we accept the control rates as valid, the probability number tells how likely we are to get as many (or more) cases as observed in a sample made up of a similar number of person-years. Roughly speaking, a probability of 0.16 indicates a difference of about 1.0 standard error and a probability of 0.05 corresponds to a difference between observed and expected of about 1.7 standard error. For mass survey samplings and biologic experimentation, a difference of 1.0 standard error is not significant, whereas 2.0 standard errors or more are statistically significant.

DISCUSSION

The incidence of pelvic malignancy following irradiation for benign gynecologic conditions varies from series to series. The elusiveness of conclusions is due to the pitfalls inherent in mass surveys of this sort. First, a suitable control group is not available. The use of expected incidence

rates in a general population such as that of Upstate New York is a compromise in that the group of patients under scrutiny has been selected because of a gynecologic disorder. The ideal control group would be one in which a group of women with benign gynecologic lesions, uncomplicated by therapy for endometrial hyperplasia, was followed up to establish the rate of pelvic malignancy, Secondly, the limitations of any data are length and completeness of follow-up, both of which are less than ideal. Thirdly, menopausal menstrual disturbances may be predisposing factors for the subsequent development of malignancy as well as the indication for irradiation.

In evaluating the data of the statistical analysis, the two critical aspects of the problem to be emphasized are the role of predisposing diseases and the role of irradiation in regard to the incidence of genital cancers. In addition, an evaluation of other pelvic and extrapelvic malignancies will be presented.

THE ROLE OF PREDISPOSING DISEASE

1. *Significance of Endometrial Hyperplasia.* The significance of this disorder in causing cancer must be carefully weighed. Randall[16] found that women with a history of menorrhagia during climacteric have a three and one-half times greater chance of developing uterine fundal cancer than do the women who experience no increased bleeding prior to cessation of their menses. Corscaden *et al.*[1] and Stander[19] noted that the number of cases of endometrial cancer in their studies exceeded the expected number by a factor of 3 to 4 and concluded, as did Randall,[16] that this reflected a predisposition of these patients to develop cancer and that radiation *per se* is not an etiologic factor. Novak and Yui[13] referred to the endometrial hyperplasia as a process possibly preceding malignant change in the endometrium. Hertig and Sommers[6] concluded that cystic hyperplasia rather than adenomatous hyperplasia was an important precursor to cancer, though both were predisposing conditions. In another series,[19] generalized hyperplasia was more predominant than cystic or interstitial hyperplasia in accounting for the majority of cancer cases.

2. *Significance of Fibroid Uteri.* Fibroid uteri were the next largest group in our series. The incidence of adenocarcinoma in myomata uteri is the same as that for non-myomatous uteri according to Randall.[16] This has been confirmed by other authors, and ranges from 1 per cent to 2 per cent. Only 1 patient in our entire series who was irradiated for myomata later developed an endometrial lesion, for a 1.0 per cent occurrence rate.

3. *Excessive Estrogen Secretion.* Excessive estrogen stimulation in menopausal irregularities is well known and underlying ovarian pathology may be present. Estrogen secreting tumors are frequently associated with adenocarcinoma of the uterus. The incidence of ovarian carcinoma may, in part, be accounted for on this basis since it is a more difficult area to examine adequately from a histologic viewpoint than the endometrium or cervix, which are readily available for biopsy.

4. *Endocrine Imbalance.* Estrogen withdrawal induced by radiation menopause may upset the anterior pituitary feed-back mechanism and lead to periods of prolonged pituitary stimulation of the endometrium and ovaries. This may in turn result in successive morphologic changes ending in cancer, according to Hertig and Sommers.[5,7]

THE ROLE OF IRRADIATION

1. *Animal Experimentation.* In alluding to Furth's[4] concept of neoplasia as an unrestrained growth, it is worth emphasizing that irradiation may not only be a mutating factor in direct permanent alteration of cells but may also act indirectly on extracytogenic forces which may lead to derangement of the balance between endocrine organs. There is evidence to suggest that this latter factor may be more important in ovarian tumorogenesis.

Irradiation of the pelvis in an attempt to induce carcinomas has been undertaken in

mice and rats. Furth[4] has stated that three basic factors are operating in ovarian tumorogenesis: (1) increase in gonadotrophes due to ovarian atrophy, (2) failure of irradiated ovarian cells to regulate the activity of gonadotrophes, and (3) disorganization of this organ initiated by injury of the ova. It is the disappearance of the ova which hastens senescence; when this occurs the hormonal status is altered and this, in turn, creates a sensitive state for tumor development. Administration of estrogens or protection of one ovary reduces the incidence of ovarian tumors. Uterine tumors have been induced by gamma rays in rabbits by Lorenz but their pathogenesis has not been determined.

2. *Low Dose versus High Dose Irradiation.* The meaning of low dose and high dose irradiation in regard to carcinogenesis has received some attention in the literature. The finding that the development of cancer was greater in the low dose irradiation group has suggested to the Roswell Park Memorial Hospital investigators a growth stimulating factor of roentgen rays. This is probably not entirely accurate but has some validity in that reaction to radiation injury leads to hyperplasia and then to neoplasia, which may not occur after high doses; *i.e.*, a large dose of radiation may eliminate the regenerative capacity of tissues completely. Ovarian tumors seem to have a threshold level (600 r) which is at the point of cessation of function.[4]

3. *The Time Lag.* The time lag of five to twenty years has been mentioned by Palmer and Spratt[15] as a factor favoring radiation as the inciting cause of carcinogenesis. Unfortunately, there are few studies of the endometrium prior to the development of adenocarcinoma in uncomplicated cases. Hertig and Sommers[6] report that the highest incidence of cystic hyperplasia was found up to thirteen years before the development of carcinoma, whereas adenomatous hyperplasia was noted one to thirteen years before the diagnosis of carcinoma. This compares reasonably well with the average time interval of eight years after irradiation and in and of itself constitutes no evidence in support of the theory that radiation rather than the underlying pathology is the cause of the carcinogenesis.

4. *Protective Effects.* It is again worth mentioning that the only sizeable series in which there was an attempt to present a control group was that of Crossen and Crossen.[3] The fact that the incidence of both ovarian and endometrial cancer was significantly lowered in irradiated, as opposed to nonirradiated, patients cannot be lightly dismissed. Rather, it emphasizes the need for similar controlled studies which, unfortunately, are most difficult if not impossible to obtain.

GYNECOLOGIC VERSUS OTHER PELVIC VISCERAL CANCERS

The gynecologic cancers have been adequately analyzed as to cervical, endometrial and ovarian neoplasms. Vaginal and vulvar lesions were absent in our series. The unusually high incidence of vaginal carcinoma found by the Roswell Park Memorial Hospital group[15] may be due to the low expected incidence figure or to the inclusion of metastatic lesions as primary cancers. This is seen in both their high and low dose category and is the only series of cases that shows this pattern.

An unexpected finding in our series was the 4 cases of colon carcinoma (excluding the 1 case which developed two months after irradiation). Three of these cases were in the sigmoid colon and 1 in the cecum; both segments are close to if not in the pelvis. No bladder carcinoma was found. The other series of lower bowel carcinomas are those of Corscaden *et al.*,[1] Stander[19] and Palmer and Spratt.[15] Stander[19] did not feel that the observed number exceeded the anticipated number by any significant degree. It is of particular interest that Palmer and Spratt's report[15] listed 7 rectal but no colon cancers. Since virtually every other category of pelvic neoplasia was high, this absence of a single case of colon neoplasm points up the difficulty in draw-

TABLE V

SUMMARIZED COMPARISON OF RESULTS OF LATE CARCINOGENESIS FOLLOWING PELVIC IRRADIATION

	Genital					Other Pelvic Sites				Total	
	Corpus	Cervix	Ovary	Vagina	Vulva	Bladder	Colon	Rectum	Anus	No.	Per Cent
Schmitz[18]	1	0	0	0	0	—	—	—	—	1	0.17
Costolow[2]	3	1	0	0	0	—	—	—	—	4	0.40
Corscaden *et al.*[1]	9	6	2	0	0	2	2	2	0	23	2.50
Crossen and Crossen[3]	4	0	1	0	0	—	—	—	—	5	0.95
Montgomery *et al.*[12]	9	2	1	0	0	—	—	—	—	12	1.40
Hunter *et al.*[8]	2	0	1	0	0	—	—	—	—	3	0.50
Palmer and Spratt[15]	29	11	8	2	1	3	0	7	0	61	8.40
Stander[19]	14	0	4	0	1	0	4	3	0	26	3.70
Rubin *et al.*	3	1	3	0	0	0	4	0	1	12	3.90
Total	74	21	20	2	2	5	10	12	1	147	

ing dogmatic conclusions about the susceptibility of a specific anatomic site.

EXTRAPELVIC TUMORS

Extrapelvic lesions such as those of the lung and larynx represent isolated instances. Breast carcinoma was below the anticipated rate in the present series as well as in that of Palmer and Spratt[15] who concluded that this showed that their series was not studied with prejudice and was not cancer prone. In Stander's study,[19] the expected number, except for breast cancer, was not encountered. There could be an argument for radiation menopause as a prophylactic measure against the development of breast carcinoma; however, this concept is neither credited nor discredited at the present stage of our clinical knowledge.

Apart from the more recent studies, no mention is made of extrapelvic tumors. The finding of 1 or 2 cases in different categories, where only a fraction of a case was expected, demonstrates one of the weaknesses of utilizing an expected-to-observed ratio rather than a probability factor. Since patients do not enter as fractions, the finding of a single case may be four to ten times the control value which forms the denominator in the ratio.

CONCLUSIONS

In concluding this survey, two questions arise:

(1) *Has irradiation of benign gynecologic malignancies resulted in the induction of pelvic malignancies?* All of the more carefully documented series are presented in a summary form in Table V. Considering the total number of pelvic malignancies, the percentage incidence varied from 0.17 per cent to 8.4 per cent. This includes not only genital cancers but bladder, colon, rectal, and anal cancers as well. The last three series are highest in incidence and this may reflect the longer average follow-up, which exceeded ten years. If Palmer and Spratt,* with the lowest response rate to their questionnaires (43 per cent), would include their whole series in the calculation, their percentage incidence would be 3.6 per cent, which is more consistent with the other two studies.

The largest single group of late tumorogenesis was endometrial carcinoma followed by ovarian and cervical carcinomas. The latter lesions, except in Palmer and Spratt's group, occurred as sporadically as vaginal and vulvar neoplasia. The opinion of most authors is that the predisposing condition rather than radiation *per se* is the etiologic factor in the gynecologic neoplasms noted. From the figures in our series, the same conclusion seems warranted.

* In a personal communication, Dr. Spratt agreed with the validity of such re-evaluation of his report.

In contrasting the tabulated figures of Palmer and Spratt[15] (Table VI) to those of Stander[19] (Table VII), which have been re-evaluated as probability figures, the two horns of the dilemma are revealed. The two studies are quite comparable in that a similar number of patients (about 700) were followed for an average of seventeen years, for approximately 12,500 patient years. The expectancy values were derived from the same source. In the Ann Arbor presentation, the probability for genital, pelvic, and combined genital and pelvic cancers is not considered highly significant. The Roswell Park Memorial Hospital experience is highly significant in virtually every category, with each showing an increased finding of cancer. The present series from Strong Memorial Hospital (Table III) falls between these two reports in significance but is more comparable to the Stander results. The need for documentation of more experiences is readily apparent.

(2) *Should radiation therapy be abandoned in treating benign conditions?* In regard to benign gynecologic conditions, one must weigh the success as well as the morbidity and mortality of surgical procedures against that of radiation therapy. It must be appreciated that the mortality from anesthesia and surgery is as high as that of late carcinogenesis. Montgomery *et al.*[12] in analyzing their experience felt that the risks with radium were less than those with surgery. The complications of benign conditions, though not lethal, can be debilitating and distressing and are difficult to weigh against the morbidity associated with treatment. This is particularly true when the complication percentage figures are so small. Few procedures are without risk in medicine but it is essential to establish these risks.

As surgery, anesthesia, and pharmaceuticals improve, radiation therapy will be used less and less for benign lesions. It should not be the fears but rather the facts which direct treatment plans. At present, the uncertainties raised by the question of late carcinogenesis have led, in part, to con-

TABLE VI

LATE CANCER INCIDENCE IN THE PALMER AND SPRATT SERIES[15]

Site	Observed		Expected		Probability
Genital					
Corpus	29		4.86		0.001
Cervix	11		6.53		0.040
Ovary	8		2.58		0.005
Vagina	2		0.17		0.020
Vulva	1		0.33		0.300
Total Genital		51		14.47	<0.0001
Pelvic					
Bladder	3		0.82		0.05
Colon	0		3.70		
Rectum	7		2.11		0.01
Total Pelvic		10		6.63	0.24
Total Genital and Pelvic		61		21.10	<0.0001
Breast	10		14.30		0.91

Conclusion: Highly significant

TABLE VII

LATE CANCER INCIDENCE IN THE STANDER SERIES[19]

Site	Observed		Expected		Probability
Genital					
Corpus	14.0		4.3		0.001
Cervix	0.0		6.7		1.00
Ovary	4.0		3.1		0.38
Vagina	0.0		0.2		1.00
Vulva	1.0		0.4		0.33
Total Genital		19.0		14.7	0.16
Pelvic					
Bladder	0.0		0.8		1.00
Colon	4.0		3.7		0.51
Rectum	3.0		2.2		0.38
Total Pelvic		7.0		6.7	0.51
Total Genital and Pelvic		26.0		21.4	0.20
Breast	9.0		13.6		0.91

Conclusion: Not highly significant

servative policies with more rigid criteria for radiation therapy in benign gynecologic lesions. The final decision in each case must be made by the referring physician and the radiotherapist. The answer will depend on their experience and philosophy, since no consistent conclusion is available in the literature.

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THE TREATMENT OF ANAL CARCINOMA BY INTERSTITIAL IRRADIATION*

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CANCER of the anus is an uncommon lesion and the problems associated with its management are somewhat overshadowed by those of rectal cancer. Treatment by interstitial irradiation has been widely practiced and at the present time, when supervoltage equipment is increasingly available, it is interesting to consider the results of treatment by this method.

CLINICAL MATERIAL

Cases Studied. At the Christie Hospital & Holt Radium Institute, from 1932 to 1955, 171 new cases were seen. This represents 0.2 per cent of all previously untreated malignant cases registered, and a rate per million of 1.8. The latter figure is low, as it is arrived at by consideration only of the number of patients referred to this hospital (in a region with a population of four and one-half million), and therefore takes no account of possible cases referred to other hospitals in the area. Roux-Berger and Ennuyer[6] reporting from the Fondation Curie stated that, out of 10,000 patients, 0.58 per cent had true anal lesions.

Of the 171 cases comprising the present study group, 34 were considered to be so advanced that no useful treatment was possible; 31 cases were referred for surgery; and 106 cases were treated by irradiation. It is this latter group with which this paper is mainly concerned (Table I).

Sex Incidence. McQuarrie and Buie[4] and Murphy[5] found a higher incidence of the disease in females; on the other hand, Sweet's[7] series of 77 cases contained more males, and Gabriel[2] reported an equal sex distribution. In this series, there are 102 males and 69 females—a ratio of almost 4:3.

Table I

CANCER OF THE ANUS

1932–1955

Number of Cases Reviewed	171
Cases Referred for Surgery	31
Cases Too Advanced for Treatment	34
Cases Treated by Irradiation	106

Age. The average age at the date of first examination was 64 years, which concurs with other published figures, *viz.*, Gabriel,[2] 61.7 years and Williams,[8] 62 years.

Histology. Cancer of the anus arises both in the modified squamous epithelium of the anal margin and lower anal canal below the pectinate line, and in the cuboidal epithelium lining the canal between the pectinate line and the anorectal ring. (This latter tissue may indeed also be modified squamous epithelium, as suggested by Goligher, Leacock and Brossy.[3]) The distribution of histologic types in the 106 cases treated by irradiation is shown in Table II.

Site. It is usual to consider cancer of the anus as arising in either the anal canal proper or at the anal margin; in this largely

Table II

FREQUENCY DISTRIBUTION BY HISTOLOGIC TYPE

Histology	No. of Cases
Carcinoma—Squamous Cell	90
Carcinoma—Transitional Cell	6
Carcinoma—Basal Cell	1
Carcinoma—Basi-squamous Cell	1
Not Apparent	2
No Section Taken	6
Total	106

* From the Christie Hospital & Holt Radium Institute, Manchester, England.

Table III

FREQUENCY DISTRIBUTION BY SITE AND SEX

Site	No. of Cases	Male	Female
Anal Margin	41	28	13
Anal Margin and Canal	48	38	10
Anal Canal	33	16	17
Anal Canal and Rectum	49	20	29

Table IV

CLINICAL STAGING OF 98 HISTOLOGICALLY PROVED TREATED CASES

Site	Clinical Stage		
	Early	Moderately Advanced	Advanced
Anal Margin	17	9	4
Anal Margin and Canal	9	13	10
Anal Canal	7	3	10
Anal Canal and Rectum	—	—	16
Total	33	25	40

retrospective study, however, it has not been possible to be so exact and the cases have been placed in four groups (Table III). This division has proved to be of some prognostic value, as will be seen later. It also confirms the belief that cancer of the anal margin is more common than cancer of the anal canal in males; the difference is, however, by no means as striking as in other reported series, such as that of Gabriel.[2]

Stage of Disease. There is no generally accepted method of clinical staging in cancer of the anus. In this series, cases have been classified as early, moderately advanced or advanced, according to the site of the lesion and the local metastatic spread (Table IV).

An interesting fact which emerged here is that the females presented at a later stage than the males. Of the 98 histologically proved treated cases, 54.5 per cent of the female group were classified as advanced compared to only 33.8 per cent of the males. This is due—in part at least—to the prevalence of cancer of the anal margin in males; it is a visible and easily palpable lesion which is likely to be noticed by the patient at a relatively early stage.

TREATMENT

The Primary Lesion. There is no general agreement on the treatment for cancer of the anus; some authorities advocate surgery, others radiation therapy. Surgery, though of potentially high curative value, necessitates in most cases a permanent colostomy, which is distressing to the majority of patients. Successful irradiation results in normal function and is, therefore, preferable whenever possible as the first treatment in cases of limited size, with surgery reserved for possible future use.

Squamous cell carcinoma of the anus of small or moderate size is curable by irradiation; it is, however, a tumor of limited radiosensitivity and this fact, added to the knowledge that the tissues of the perineal region are notoriously intolerant to high dose irradiation, means that great care must be taken in planning treatment. External irradiation to radical dosage results in a reaction which is extremely painful and, if taken to curative levels, carries a high risk of tissue necrosis. Williams[8] reported 23 cases of carcinoma of the anal canal treated by supervoltage roentgen therapy of which 5 developed serious radiation necrosis.

We consider that, as will be shown later, the results of interstitial irradiation justify this as the method of choice for limited anal lesions. In the case of extensive lesions—and these include most of our 49 cases classified as anal canal and rectum carcinomas—radiation therapy will almost certainly fail and will seldom produce worthwhile palliation; an increasing awareness of this has resulted in fewer such cases being treated in this hospital in recent years.

The majority of the interstitial treatments consisted of single plane and two plane implants; occasionally, particularly in the earlier years, volume implants were

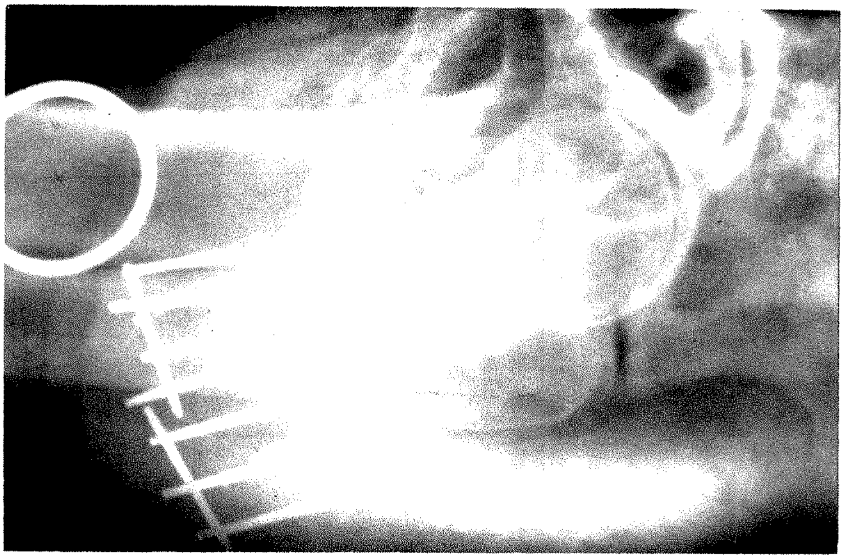

Fig. 1. Single plane radium needle implant, lateral view.

performed for rather large lesions and were sometimes combined with intracavitary radium. Most of these latter cases did badly and the method has fallen into disuse, though not, perhaps surprisingly, because of a high incidence of necrosis, but rather because of its inability to cover adequately the whole tumor area.

For small unilateral lesions a single plane implant is employed, aiming at a dose of 6,000 r_γ in seven days (Fig. 1). For thicker lesions, or those involving both sides of the anus, a two plane implant is necessary; the dose should not be more than 5,500 r_γ in seven days (Fig. 2, *A* and *B*).

Lymph Node Metastases. The lymphatic drainage of the anal margin and canal is predominantly to the superficial inguinal lymph nodes, though some of the upper lymphatics of the canal drain directly to the anorectal or hypogastric lymph nodes.[1] Of the 98 histologically proved cases in this series, 24.5 per cent had clinically significant lymph node involvement in the inguinal region within three months of the first examination and the incidence by site is shown in Table v. In 2 cases, both groins were involved.

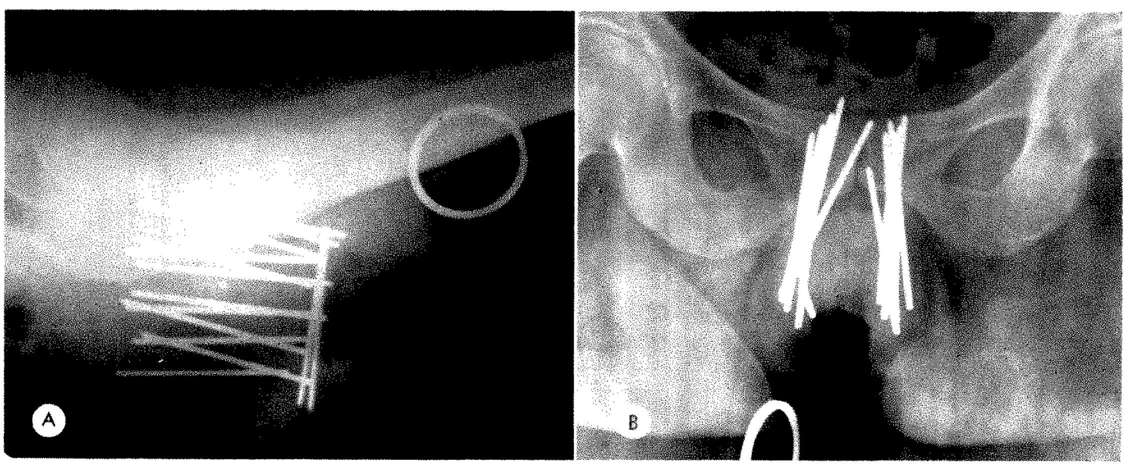

Fig. 2. Two plane radium needle implant. (*A*) Lateral view and (*B*) anteroposterior view.

Table V

LYMPH NODE INVOLVEMENT IN 98 CASES WITHIN THREE MONTHS OF FIRST EXAMINATION

Site	No. of Cases	Cases with Lymph Node Involvement	
		Number	Per Cent
Anal Margin	30	3	10.0
Anal Margin and Canal	32	11	34.4
Anal Canal	20	3	15.0
Anal Canal and Rectum	16	7	43.8

Mobile involved inguinal lymph nodes are best treated by block dissection of the groin. The results of irradiation are so poor that this method should never be preferred to surgery in potentially curable cases; it is indeed very doubtful if the treatment of even inoperable lymph node involvement by irradiation achieves any palliation in a sufficient number of cases to justify its use.

MANAGEMENT

The management of the patient prior to, during and after implantation of radium is very important and we have thought it worthwhile to describe the routine care of a case as undertaken at this hospital. Admittance is arranged three days before the implantation is to be done. The patient is given a very light diet and an aperient is administered on the first evening, followed by enemas on the second and third days, with a final bowel washout the afternoon of the third day. The night before operation, the patient is given 30 min. tinct. opii and on the morning of operation this is repeated; during the first six days of a seven day implant, 20 min. tinct. opii is administered twice a day. With this regime it is nearly always possible to keep the patient constipated throughout the time the radium needles are in position. On the seventh day and the day following removal of the radium needles, the patient is given petrol agar twice daily. This usually results in a resumption of normal bowel habit—if not, a glycerine suppository is given.

The patient is nursed on the side with a thin pillow between the knees and anal swabbing with a bland solution such as sodium bicarbonate is carried out up to three times daily; an antibiotic is not routinely given. After removal of the radium needles, the patient is given a bath twice daily, with swabbing of the perineum after each bowel action. The length of time spent in the hospital is three to five weeks depending on the size of the implant and the severity of the reaction. It is essential to instruct the patient in the importance of regular bowel movement—so often there is a tendency to constipation because of the discomfort following treatment, and petrol agar is often necessary for some time. If control of defecation is good prior to treatment, there is usually no reason to expect deterioration afterwards.

COMPLICATIONS

Local tissue necrosis is the complication to be feared after irradiation of anal cancer. Of 98 histologically proved treated cases available for three year follow-up, 23 (or 23.4 per cent) developed such a necrosis. Of these, only 10 were of a serious nature, 6 requiring colostomy and 4 excision. The remainder healed satisfactorily after a period of nursing sometimes combined with light diathermy. Anal stricture of a marked degree occurred in only 1 case.

RESULTS

Of the 106 cases treated by irradiation, 6 were regarded as incurable from the beginning and received only palliative treatment; these cases have been excluded from the series when assessing results. Also excluded are 8 cases not histologically proved. For analysis there are 92 cases and the survival at three, five and ten years is shown in Table VI.

In a series containing a high proportion of old people, which is the case in cancer of the anus, some form of corrected rate is desirable, since deaths from causes other

Table VI

SURVIVAL RESULTS OF RADICAL TREATMENT

Interval (yr.)	No. of Cases	Survival		
		No. of Survivals	Crude Rate (per cent)	Age Corrected Rate (per cent)
3	92	46	50.0	55.2
5	85	37	43.5	51.2
10	61	17	27.9	50.7

than cancer of the treated site occur at an accelerated rate as the after-treatment interval lengthens.

The age corrected method of calculation first suggested by Berkson in 1942, approved by the World Health Organization Sub-Committee on Registration of Cancer in 1950 and discussed and applied in the Third Statistical Report from the Christie Hospital & Holt Radium Institute in 1950 has been used to correct for the number of deaths that would be expected to occur under prevailing conditions of mortality in a population having the same sex and age distribution as the treated series. This rate may be expressed as:

$$S.R._{cor.} = \frac{\text{Number alive and treated after } n \text{ years}}{\text{Expected number of survivors after } n \text{ years}}$$

The results analyzed by site and stage are shown in Tables VII and VIII. Cancer of the anal margin has the best prognosis; metastatic spread to lymph nodes is uncommon and the highest percentage of early cases was found in this group. However, with such small numbers of cases, the difference in percentage survival is not satistically significant. Study of those cases either presenting with clinically evident involvement of inguinal lymph nodes or developing it within three months reveals that all but 2 of the cases are dead: 8 further cases developed metastatic lymph nodes later, and none survived. It is evident that the prognosis of cases with regional lymph node deposits is extremely poor.

Surgery for residual or recurrent cancer was undertaken in 21 of the 92 radically treated cases, and 13 of the 21 are alive and well three years later.

Table VII

FIVE YEAR SURVIVAL RESULTS ANALYZED BY SITE

Site	No. of Cases	Survival	
		No. of Survivals	Age Corrected Rate (per cent)
Anal Margin	26	14	63.4
Anal Margin and Canal	31	14	53.2
Anal Canal	15	6	47.1
Anal Canal and Rectum	13	3	27.2

Table VIII

FIVE YEAR SURVIVAL RESULTS ANALYZED BY STAGE

Clinical Stage	No. of Cases	Survival	
		No. of Survivals	Age Corrected Rate (per cent)
Early	31	19	72.2
Moderately Advanced	20	11	64.8
Late	34	7	24.3

CONCLUSION

Treatment of cancer of the anus by interstitial irradiation, with surgery in reserve, has yielded a five year corrected survival rate of 51.2 per cent. This has been achieved in the majority of cases with the preservation of normal function, and with careful planning the complications have not been severe. For early and moderately advanced lesions, radium implantation provides a satisfactory method of treatment.

SUMMARY

There were 171 cases of cancer of the anus seen at the Christie Hospital & Holt Radium Institute from 1932 to 1955 and these are reviewed. Treatment by interstitial irradiation, with surgery in reserve, has

been employed in the majority of cases and the results of this treatment are presented.

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LYMPHOSARCOMA: SURVIVAL AND THE EFFECTS OF THERAPY*

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THE therapeutic regimen of choice for patients with lymphosarcoma is predominantly that of radiation therapy. This has been true for many years and has remained so despite the initial impression that alkylating agents, anti-metabolic drugs and adrenal steroids might be more valuable in the control of the disease.[1,3,4,6,14,24,30] In order to arrive at such a conclusion, it has been of benefit to objectively review the therapeutic results over a period of years at one institution.

Over a thirty year period numerous patients with lymphosarcoma have been treated at the Memorial Center for Cancer and Allied Diseases. Histologic criteria for diagnosis have been strict and constant.[3,6,8,26,30] The experience has been that of one institution, largely under the direction of one physician (L.F.C.), and has recently been critically reviewed.[27]

This report presents the information derived from this analysis as it pertains to the effects of therapy and survival. Data describing the histologic classification, transitions of the disease, and age and sex distribution of the group will also be presented.

MATERIAL

Case selection. All hospital and out-patient records from 1928 to January 1, 1958 bearing the diagnoses of lymphosarcoma, reticulum cell sarcoma or giant follicular lymphosarcoma were carefully studied. To allow at least a five year period of follow-up, only those patients whose clinical onset of disease occurred prior to January 1, 1953 were included in this analysis. A total of 1,635 charts were reviewed. Of these, 366 were excluded, usually because of the lack of conclusive tissue examination at this institution or because of obvious lymphatic leukemia at the first visit.

Table I

HISTOLOGIC TYPES OF LYMPHOSARCOMA (1,269 CASES)

Giant Follicular Lymphosarcoma	162
Lymphosarcoma	553
Reticulum Cell Sarcoma	554
Total	1,269

The remaining 1,269 cases comprise the study group, material from which will be presented in this report. This group includes not only cases designated and filed as generalized lymphosarcoma, but also those cases which could be located under lymphosarcoma filed under such regional classifications as malignant lesions of the tonsil, stomach, bone, skin, mediastinum, etc.

HISTOLOGIC CLASSIFICATION

The histologic classification of these tumors is not uniform, not only from institution to institution, but also from pathologist to pathologist within one institution and probably also for the same pathologist over a period of years.[10–12,16,21 25,32,33] Therefore, we have chosen to utilize the general subdivisions shown in Table I.[3,8,26,30] These diagnoses were either rendered by a senior member of the Pathology Department of Memorial Center or were accepted after review by Drs. John Berg and Stephen Sternberg.

* From the Lymphoma Service, Department of Medicine, Memorial Center for Cancer and Allied Diseases; the Lymphoma Section of the Division of Clinical Chemotherapy, Sloan-Kettering Institute for Cancer Research; and the Department of Medicine, Cornell University Medical College, New York, New York.
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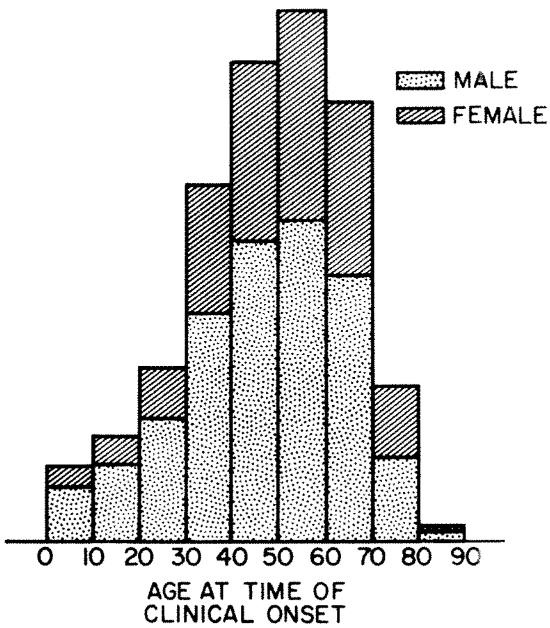

FIG. 1. Age and sex distribution of 1,269 cases of lymphosarcoma.

AGE AND SEX DISTRIBUTION

The diseases are more frequent in males than in females in all age groups, the average ratio being 1.7 to 1.0. Figure 1 shows the age and sex distribution of the entire group. The age range, at the time of the clinical onset of the disease, extends from 22 months to 92 years. The greatest number of cases is seen during the fifth decade of life and the median age for the entire group

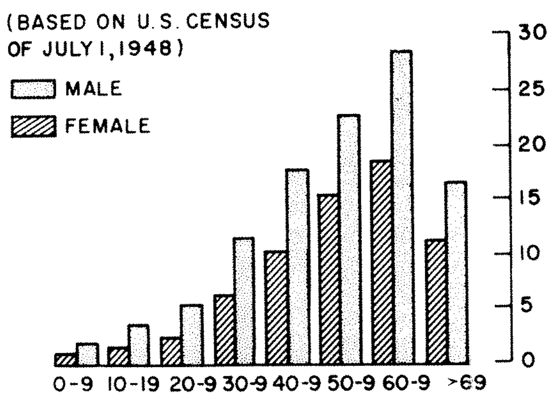

FIG. 2. Relative incidence of 1,269 cases of lymphosarcoma. (Rates are arbitrary based on the United States census taken at the approximate midpoint of this study.)

is 49.7 years. Figure 2 shows the relative incidence of disease, relating the number of cases to the United States population figures for the approximate midpoint of the study and demonstrating the increasing relative incidence with age, except for the oldest age group.

TRANSITIONS TO LEUKEMIA

There is much confusion and disagreement concerning the interrelationships between these tumors of lymphoid origin and lymphatic leukemia.[2,6,17,28,32,33] Such terms as leukosarcoma, leuko-lymphosarcoma, lympho-leukosarcoma and reticulum cell leukemia have been proposed for the frequent, apparent leukemic transformations occurring in this group of diseases. These terms are meaningful chiefly to those who have defined them and there is little uniformity of usage. The therapeutic implications, however, of the generalization of the disease as manifested by a leukemic change make it necessary for the physician to recognize such a transformation. It is the recognition that this transition can occur which is important, rather than the name applied to it.

As indicated by Table II, 7.6 per cent of the total group demonstrated leukemic changes. This occurred more often in children than in adults. The change was seen less often in reticulum cell sarcoma than in the other histologic categories. Acute blastic leukemia was seen only 10 times, and with a higher incidence in children than in adults, the adult disease more often being chronic lymphatic leukemia. There is a group of patients who show atypical leukemic pictures, often with recognizable sarcoma cells in the bone marrow and peripheral blood. The definition of this group is an arbitrary one and we have used the term leuko-lymphosarcoma for this category.

RESULTS OF THERAPY

The value of radiation therapy in the treatment of patients with lymphosarcoma is well established.[3,4,6,30] The comparative radiosensitivity of these tumors generally

Table II

FREQUENCY OF LEUKEMIC CHANGES IN PATIENTS PRESENTING INITIALLY WITHOUT LEUKEMIC CHANGES

Initial Diagnosis	No. of Cases	Acute Leukemia		Chronic Lymphatic Leukemia		Leuko-lympho-sarcoma		Total	
		No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Giant Follicular Lymphosarcoma	162	2	1.2	5	3.1	7	4.3	14	8.6
Lymphosarcoma	553	6	1.1	25	4.5	39	7.0	70	12.6
Reticulum Cell Sarcoma	554	2	0.4	4	0.7	7	1.3	13	2.4
Total	1,269	10	0.8	34	2.6	53	4.2	97	7.6
Children	69	5	7.2	0	0.0	4	5.8	9	13.0
Adults	1,200	5	0.4	34	2.8	49	4.1	88	7.3

permits some degree of symptomatic improvement, but it is not known whether this treatment has significantly prolonged survival.

Many other agents have been used and some have received enthusiastic support. At intervals, interest has been renewed in the possibility of surgical cure in certain localized forms of lymphosarcoma.[4,9,15,29]

It is difficult to compare the results of different forms of treatment in a chronic disease which has a highly variable natural history and for which there is no cure. No studies have been reported, nor is the present review an example, of a randomized, well-controlled, concurrently running analysis and comparison of different therapeutic regimens. However, an attempt has been made to study the therapeutic results observed during the thirty year period of this review.

Figure 3 shows the results obtained with the five agents used most frequently during the period of this study. By "complete" response is meant complete freedom from grossly detectable disease for a period of at least one month after the completion of, or while receiving, therapy. All other instances of objective regression, lasting for a period of at least one week without concomitant spread of disease eleswhere, were classified as "partially" benefited. If systemic therapy was given with irradiation, benefit was not attributed to the drug unless areas of disease not treated with radiation showed improvement.

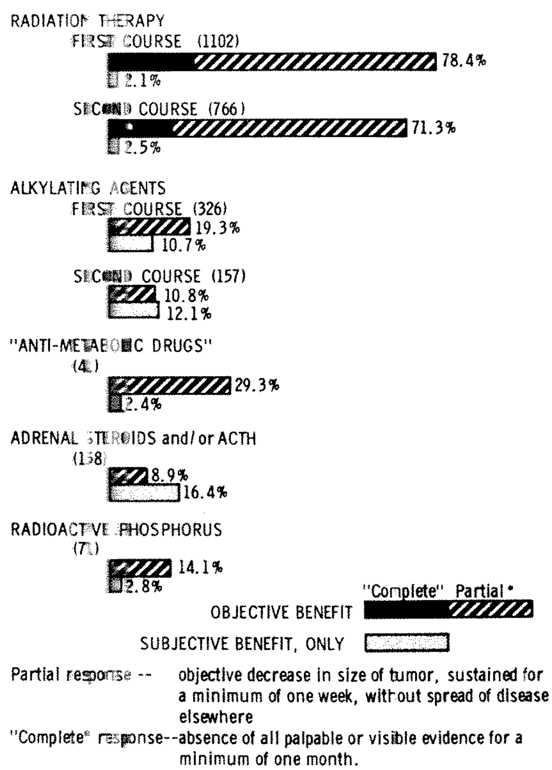

Fig. 3. Analysis of response to treatment of lymphosarcoma.

RADIATION THERAPY

The first course of radiation therapy resulted in objective improvement in 78.4 per cent of the 1,102 patients treated; in over 20 per cent the benefit was classified as "complete." The second course of therapy gave almost equal results. In general, the same degree of response noted during the first course of radiation therapy was observed after the second. In most cases, the usefulness of radiation therapy was eventually limited by the generalized spread of the disease, by increased radioresistance of the tumor, and diminished tolerance of the patient.

ALKYLATING AGENTS

Since the early 1940's, nitrogen mustard and related drugs have been extensively employed in patients with tumors of lymphoid origin.[5,13,18] Though several experimental agents were used in this series of patients, the great majority received either HN-2 (methyl-bis[beta-chloroethyl]-amine) or TEM (triethylene melamine).

Objective benefit, not attributable to simultaneously administered radiation, was observed in 19.3 per cent of patients after the first course of treatment, and in 10.8 per cent after the second. In only 2 instances did this improvement meet the criteria of complete benefit.

ANTI-METABOLIC DRUGS

A total of 41 patients of this group received various folic acid or purine antagonists. Objective benefit, partial only, was recorded in 29.3 per cent. Ten patients had leukemic changes before the use of antimetabolic drugs. Seven of the 10 did not respond; the remaining 3 had a partial improvement.

ADRENAL STEROIDS AND ACTH

Soon after it became known that stimulation of the adrenal gland or the administration of adrenal steroids had a deleterious effect on lymphatic tissue, these agents were used in the treatment of lymphosarcoma, with reported benefit in some patients.[24] In addition to their effects on the tumor, these agents may achieve symptomatic improvement, albeit temporarily, by suppressing pain and fever and by restoring in some measure lost weight, strength and a sense of well-being.

One hundred and fifty-eight patients received this type of therapy, the majority since 1950. Many of these patients had advanced disease and had received several courses of radiation therapy and antitumor chemotherapy. Though further chemotherapy in such cases was often contraindicated by hematopoietic depression, some form of treatment was demanded by continuing or recurrent constitutional symptoms. Adrenal steroids and ACTH were used most often in such patients in an attempt to improve the quality of their survival. In 8.9 per cent, partial benefit resulted. This benefit was objective, but usually brief, rarely lasting more than several weeks.

The patient with lymphosarcoma who develops a frank hemolytic anemia may be materially benefited by the use of adrenal steroids and ACTH, and sometimes temporary improvement is seen in the hemorrhagic manifestations of patients with profound thrombocytopenia.

RADIOACTIVE PHOSPHORUS

The use of radioactive phosphorus in the treatment of lymphosarcoma initially received enthusiastic support, but it is now generally restricted to those patients showing the transition to chronic lymphatic leukemia.[7,19,20,23] Seventy-one patients with lymphosarcoma were treated with radioactive phosphorus during the period of this study, 14.1 per cent showing objective improvement.

COMBINATION THERAPY

In certain situations, the intravenous administration of a rapidly acting alkylating agent immediately prior to radiation therapy is indicated. These are instances in which radiation therapy alone can aggravate the precarious state of patients with

TABLE III

CASES TREATED SURGICALLY

Surgical Procedure	Giant Follicular Lymphosarcoma	Lymphosarcoma	Reticulum Cell Sarcoma	Total
Neck Dissection	2	6	11	19
Axillary Dissection	1	1	5	7
Groin Dissection		1	1	2
Supraclavicular Dissection			1	1
Gastrectomy		9	12	21
Bowel and Lymph Node Dissection		2	3	5
A-P Resection			1	1
Pelvic Exenteration		1		1
Head and Neck Procedure		2	4	6
Amputation			11	11
Wide Skin Excision	1		1	2
Total	4	22	50	76

tumor compression of the superior vena cava, trachea or spinal cord. The alkylating agent seems to allow the use of larger and more frequent increments of radiation.

RADICAL SURGERY

We have evaluated the results of surgical attempts to eradicate lymphosarcoma. Such an evaluation should be interpreted with the realization that this is a retrospective study. These groups were not randomly selected and undoubtedly are not entirely comparable. Surgical procedures were usually attempted for only very early, well-localized disease. Seventy-six such procedures were accomplished in this group of patients and are summarized in Table III.

Table IV compares the end results and five year survivals of these patients with those who had the same extent of disease treated by nonsurgical methods, predominantly radiation therapy. These data indicate that the nonsurgically treated group with Stage I disease did significantly better

TABLE IV

COMPARISON OF RESULTS WITH SURGICAL AND NONSURGICAL MANAGEMENT

	Stage I Lymphosarcoma		Stage II Lymphosarcoma	
No. of Cases	217		396	
% Treated with Surgery	24%		6%	
	Surgery	Other Therapy	Surgery	Other Therapy
No. of Cases	52	165	23	373
End Results (per cent)				
Dead of disease	67.3	44.2	74.0	68.1
Dead of ?	5.8	10.9	4.3	10.4
Lost, with disease	5.8	2.4	0.0	4.6
Lost, NED*	7.7	12.7	13.0	3.0
Alive, NED*	13.5	21.2	8.7	5.6
Five Year Survivals (per cent)	28.8**	52.2**	13.0	23.9

* No evidence of disease for over one year.
** P equals less than 0.01.

Table V

ANALYSIS OF CASES WITH RADICAL NECK DISSECTION

Case No.	Age	Sex	Diagnosis	Stage	Roentgen Therapy	Recurrence (mo.)	Duration (mo.)	End Result
0734	41	M	RCSA	II	No	Unknown	1*	Dead of disease
1045	11	M	RCSA	II	No	1	4	Dead of disease
1073	3	F	LSA	I	No	1	4	Dead of disease
0329	49	M	LSA	II	No	2	5	Dead of disease
1152	60	M	RCSA	I	No	1	7	Dead of disease
1146	13	M	LSA	II	Yes	2	10	Dead of disease
1164	50	M	RCSA	I	Yes	8	13	Dead of disease
0668	11	M	RCSA	II	No	4	16	Dead of disease
1166	52	M	RCSA	I	No	9	16	Dead of disease
0614	34	M	RCSA	I	No	10	17	Dead of disease
0659	51	F	RCSA	I	No	21	28	Dead of disease
1153	50	F	LSA	I	No	Unknown	38	Dead of ?
0932	58	F	GFLSA	O	No	24	80	NED**
1107	69	M	LSA	I	No	11	88	Dead of disease
1239	54	M	RCSA	II	No	None	93	NED**
1115	19	M	LSA	II	Yes	7	94	Lost, NED**
0951	40	M	GFSLA	I	No	None	168	NED**
1109	11	F	RCSA	I	Yes	17***	203	NED**
1116	40	M	RCSA	I	Yes	6	291	NED**

* Operative morbidity and mortality, with hemorrhage, nerve injury and pneumothorax.
** No evidence of disease for one year or more, at last evaluation.
*** Second partial radical neck dissection on opposite side for recurrent tumor, with postoperative roentgen therapy.
Note: RCSA = reticulum cell sarcoma; LSA = lymphosarcoma; GFLSA = giant follicular lymphosarcoma.

than those treated with surgery. The data are less conclusive in the groups with Stage II disease, though the tendency is again in favor of the nonsurgically treated patients.

The entire story, however, is not told from the over-all survival figures. Table V lists the 19 patients who underwent radical neck dissections. Six patients of this group have survived for long periods without evidence of disease. Three of these patients received radiation therapy to the surgically treated area, postoperatively. Of this group of 6 patients, the disease recurred in other sites in 4 instances from seven to twenty-four months after surgery. In 3 cases, radiation therapy has controlled the disease for periods of five to twenty-five years. The fourth patient underwent a partial radical neck dissection on the opposite side with postoperative irradiation and is now well over fifteen years later.

It is concluded from this analysis that radiation therapy remains the treatment of choice in this group of diseases because of the high degree of radiosensitivity of these tumors and the frequency of multicentric foci of lymphosarcoma in clinically well-localized disease.

COMPLICATIONS OF THERAPY

In the final evaluation of any therapy, the frequency of serious complications (Table VI) must be compared to the expected frequency of benefit.

Of the 1,102 patients who received radiation therapy, 21, or 1.9 per cent, developed severe complications. These were radiation osteitis, persistent and severe radiation pneumonitis and fibrosis, severe skin ulcerations requiring plastic surgical repairs, severe iritis and glaucoma and aggravation of tracheal and superior vena cava obstruction.

The use of alkylating agents resulted in irreversible bone marrow damage in 3.1 per cent of those who received these drugs.

In addition, 2 patients who received nitrogen mustard developed severe uric acid nephropathy; 1 of these being fatal.

Bone marrow aplasia was encountered in 1 patient, or 2.4 per cent, of the group which received anti-metabolic drugs. Another patient, who was given four courses of 6-mercaptopurine, developed jaundice with each course of treatment, and at postmortem had extensive postnecrotic cirrhosis without tumor.

Adrenal steroids or ACTH were given to 158 patients in this series. A total of 16, or 10.1 per cent, developed complications thought to be directly related to this therapy. There were gastrointestinal ulcerations, usually unsuspected, overwhelming moniliasis or bacterial infections, moderate to severe psychoses, severe osteoporosis with fractures and aggravation of diabetes and congestive heart failure. These complications occurred despite the use of available preventive measures.

Ten, or 13.1 per cent, of the 76 patients who underwent radical surgery developed severe postoperative complications. In 8 of these instances, these complications appeared to be the direct cause of death.

Of the 71 patients who received radioactive phosphorus, 11, or 15.5 per cent, developed irreversible bone marrow depression or aplasia.

END RESULTS AND SURVIVAL CURVES

In order to evaluate the survival curves and to determine what differences, if any, can be shown to exist between various subgroups, the survival percentages have been plotted on log-probability paper, as shown in Figure 4. The data have been plotted as per cent survival after the clinical onset of disease as well as duration from the first Memorial Center visit. Plotted in this way, these data are linear over a wide range about the median and allow a better estimate of the median duration of disease than would be available from the crude data. The level of significance of difference between the two curves can be determined by applying the "t" test to differences in median survival, as determined from the most objective data, that is, from the duration of life after the first Memorial Center visit.[22,31]

Table VI

FREQUENCY OF THERAPY COMPLICATIONS

Therapy	No. of Cases	Complications (per cent)
Radiation	1,102	1.9%
Alkylating Agents	326	3.7%
Anti-Metabolic Drugs	41	4.9%
Steroids and/or ACTH	158	10.1%
Radical Surgery	76	13.1%
P^{32}	71	15.5%

Table VII shows the survival data for the various subgroups studied. All information was taken from survival curves as described above. The data from the clinical onset of disease shed some light on the natural history of lymphosarcoma in various settings. The data from the first Memorial Center visit are more accurate for statistical purposes and are comparable, one group to another. Yet, they do not describe the course of the disease, as the onset always antedated the first hospitalization

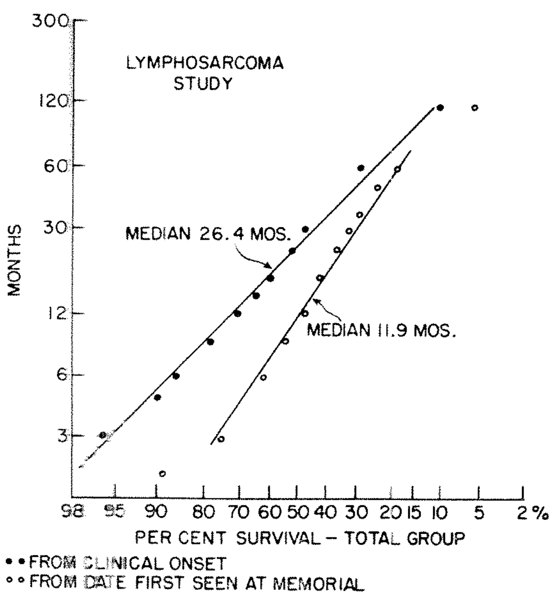

Fig. 4. Survival curves of 1,269 patients with lymphosarcoma. (Plotted on log-probability paper.)

TABLE VII

VARIOUS COMPARISONS OF SURVIVAL DATA

Groups Compared	No. of Cases	From Clinical Onset			From First Memorial Work-up		
		Two Years (per cent)	Five Years (per cent)	Median* (mo.)	Two Years (per cent)	Five Years (per cent)	Median* (mo.)
Total	1,269	52.5	28.4	26.4	35.2	18.5	11.9
Age							
0–15	69	23.2	17.4	7.5	17.4	13.0	3.9?
16–92	1,200	54.2	29.0	27.7	36.3	18.8	12.6
Male	790	50.4	26.5	24.2	34.4	17.3	10.5
Female	479	57.1	32.2	32.8	36.5	20.4	13.2
Giant Follicular Lymphosarcoma	162	85.2	54.4	72.0	64.8	33.9	48.0
Lymphosarcoma	553	51.3	27.0	25.2	35.8	18.6	11.7
Reticulum Cell Sarcoma	554	44.1	22.6	21.4	26.0	13.9	8.2
Stage							
O–I	245	66.3	46.6	51.0	55.7	40.7	34.5
II	397	44.9	23.2	22.2	30.8	17.7	10.5
III	627	52.0	24.5	25.5	30.0	10.4	8.4
1928–1934	95	53.1	29.2	26.8	34.8	17.9	12.8
1935–1939	122	57.8	34.7	28.7	42.7	26.2	18.1
1940–1944	274	53.3	29.6	27.8	36.2	22.6	13.2
1945–1949	385	47.6	26.0	22.6	34.6	19.5	10.6
1950–1952	309	51.8	25.9	26.6	36.8	15.5	11.4

* Medians from curves of all data were plotted on log-probability paper.

and the diagnosis in most cases was made prior to this date.

Certain observations concerning survival can be emphasized by the survival curves, as presented in Figures 5 through 9.

The disease in children is more rapidly fatal than in adults. Though 17.4 per cent of the children do survive five years or more, when the disease takes a downhill course, it does so at an accelerated rate.

As is well known, giant follicular lymphosarcoma is a much more benign disease than the other two groups. The group of patients with small cell lymphosarcoma survive slightly, but significantly, longer than the group with reticulum cell sarcoma.

It is interesting to note that female patients do somewhat better than male patients, as measured by survival rates. This is true for all age groups, but it is not evident for the group with giant follicular lymphosarcoma.

As would be expected, those patients with localized disease at the time of their first Memorial Center visit survive much longer than those with clinical Stage II or Stage III disease; however, the difference in survival between the latter two stages is not significant at the 5 per cent level.

Since the early 1940's new agents have been introduced for the treatment of lymphoid tumors. The alkylating agents, anti-metabolic drugs and adrenal steroid therapy have at one time or another received enthusiastic support. Great advances in blood replacement and the treat-

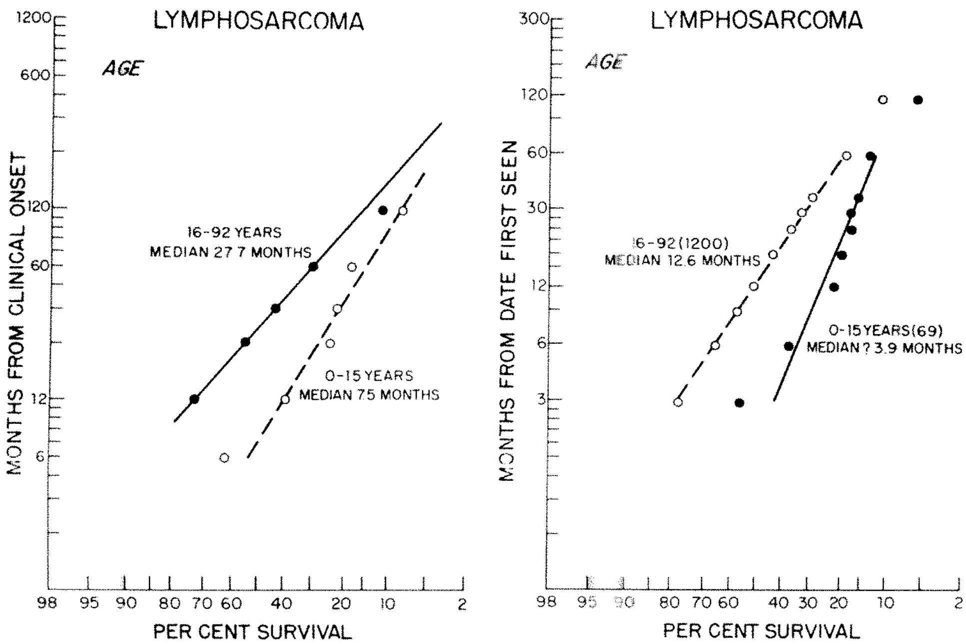

Fig. 5. Lymphosarcoma survival curves, children compared to adults.

ment of bacterial infections should have contributed to the longer survival of patients with lymphosarcoma.

Survival curves were analyzed as a function of the year of admission to Memorial Center. These curves (Fig. 9) indicate that no improvement in survival has resulted since 1928. Only the period from 1935 to 1939 stands out as showing better results than all periods before and after. Even this improvement is only slight. It is difficult to know whether changing diagnostic criteria

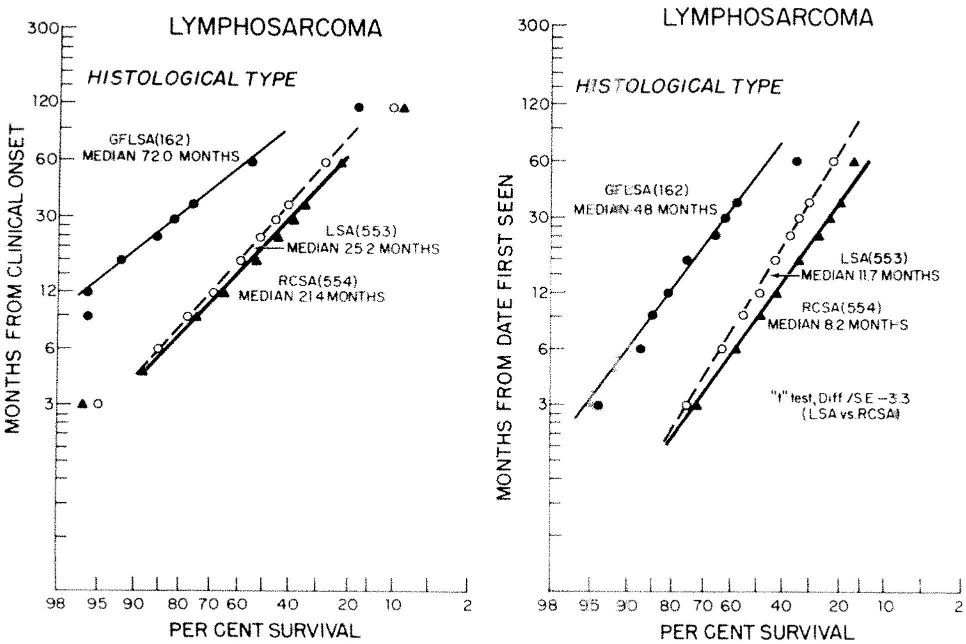

Fig. 6. Lymphosarcoma survival curves, histologic types compared.

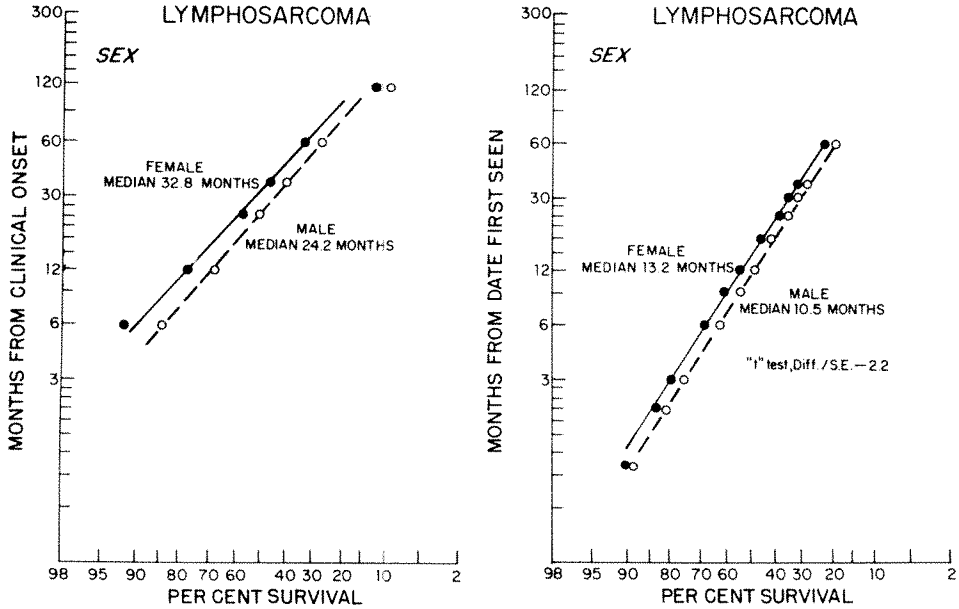

FIG. 7. Lymphosarcoma survival curves, male compared to female.

over the years or an increasing percentage of critically ill patients in recent years has influenced these results.

It is unfortunate that we have no group of nontreated patients to compare with those who received radiation therapy. However, it would appear that radiation therapy can provide as good results, measured by survival, as the newer agents introduced since 1940. Gross survival curves do not provide information concerning the quality of survival. We have all seen isolated cases of substantial improvement after the administration of the

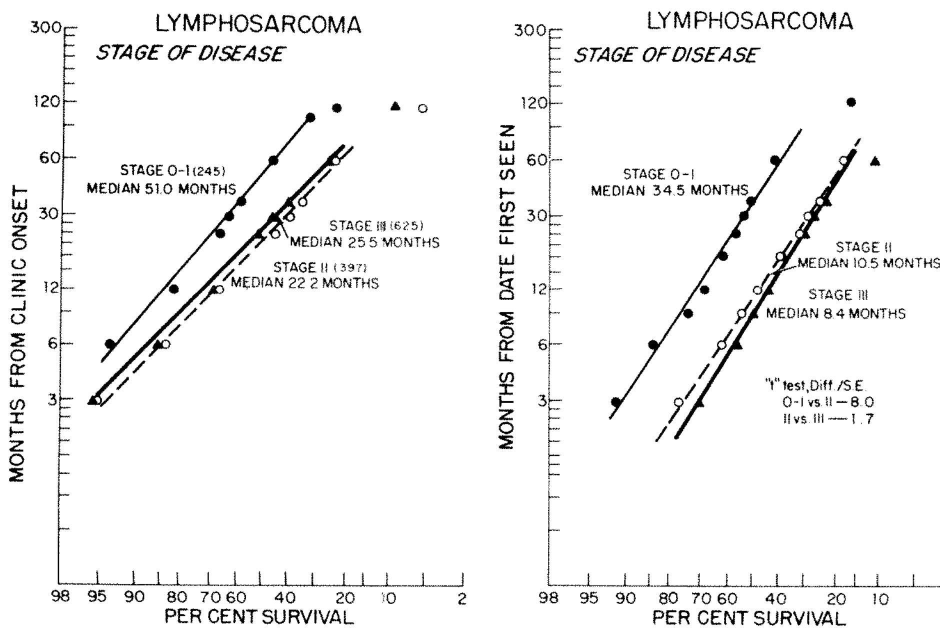

FIG. 8. Lymphosarcoma survival curves, comparison according to stage of disease on admission.

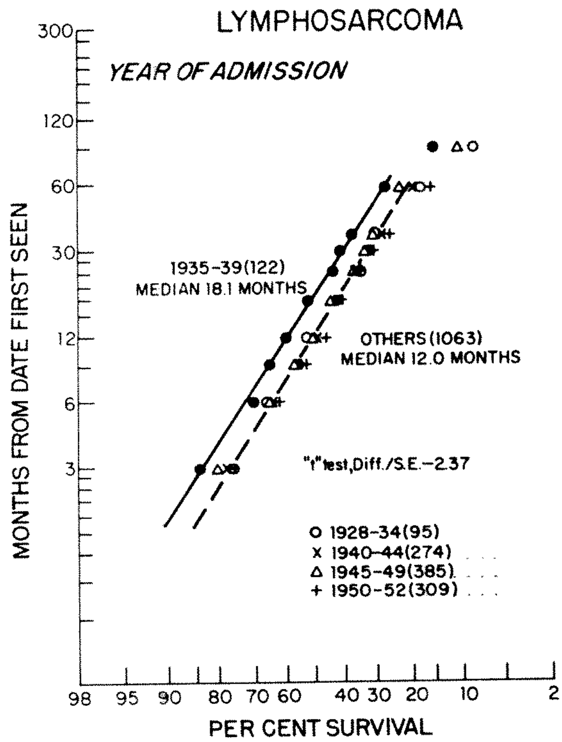

Fig. 9. Lymphosarcoma survival curves, comparison according to the year of admission to Memorial Center.

newer therapeutic agents. Specific problems such as superior vena cava obstruction and spinal cord compression undoubtedly respond more quickly and more safely with combination therapy than with irradiation alone. Therefore, we are not entirely justified in evaluating the new therapeutic agents on the basis of an analysis of gross survival data only.

SUMMARY

A review has been completed of the experience at Memorial Center for Cancer and Allied Diseases with the group of diseases known generally as lymphosarcoma. All histologically proved cases were studied as of January 1, 1958, if they had been admitted to this institution between 1928 and 1953, thus providing a five year follow-up period.

Histologic diagnoses were divided into three groups: giant follicular lymphosarcoma, 162 cases; lymphosarcoma, 553 cases; and reticulum cell sarcoma 554 cases. Patients with manifest leukemia when first seen at this institution were excluded.

The age and sex distributions indicate a median age for the entire group of 49.7 years and a ratio of males to females of 1.7 to 1.0.

A leukemic transition was noted in 7.6 per cent of the entire group and was related to the patient's age and the histologic classification.

The objective and subjective response to treatment is presented for radiation therapy, 1,102 cases; alkylating agents, 326 cases; anti-metabolic drugs, 41 cases; adrenal steroids and/or ACTH, 158 cases; and radioactive phosphorus, 71 cases. The frequency of complications of therapy is also presented.

Seventy-six patients who underwent radical surgery are compared to those with comparable disease who received non-surgical treatment.

The over-all five year survival rate, from clinical onset, of patients with lymphosarcoma is 28.4 per cent. The median survival from clinical onset is 26.4 months. The survival figures as affected by the histologic group, age, sex, stage of disease, and year of admission are presented.

It is concluded that radiation therapy remains the treatment of choice for lymphosarcoma and that no increase in survival can be demonstrated over a period of twenty-five years, despite the addition of antibiotics, steroids, and alkylating agents to the therapeutic program of conventional radiation therapy.

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SKIN AND SUBCUTANEOUS REACTIONS INDUCED BY SUPERVOLTAGE IRRADIATION*

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SUPERVOLTAGE gamma[25,34] and roentgen-ray radiations induce skin and subcutaneous reactions in far greater frequency and intensity than has been indicated in the literature.[5,9,17,27,31,32]

In contrast to the analyses in the past detailing skin reactions secondary to the use of conventional roentgen rays,[3,35] few papers describe and evaluate the skin reactions of high energy radiation.[5,8,9,27,31,32] Only general impressions on subcutaneous reactions have been published.[16,18,20,33]

The statement of Failla *et al.*[16] that "with higher dosages the limiting factor may become the tolerance of the subcutaneous tissue" is substantiated by the cases of subcutaneous fibrosis reported in this paper. They measured surface doses of supervoltage radiations with an extrapolation ionization chamber.[15]

The skin sparing characteristics of supervoltage therapy have been abundantly emphasized.[8,9,10,13,14,18,20,22,25,33,36] There are clinical reports of extensive supervoltage experience that practically disregard immediate superficial reaction.[4,13] One states that "no subcutaneous reaction at all has been met with in an extensive series over a five year period."[4]

The skin sparing of supervoltage radiation has come to mean spared skin in an absolute sense. We, on the other hand, have had supervoltage roentgen- and gamma-ray experience to the contrary and will attempt to place the matter of supervoltage integumental reactions in proper perspective by offering a detailed analysis. Unless the various factors[3,6,11,14,16,29,30,31,33] to be presented herein are included when reporting skin and subcutaneous reactions, the validity of the observations made can be challenged.

With the increased use of supervoltage modalities, fewer[5,9,10,23,31] rather than more[8,14,19,21] radiation equipment and surface dosage factors are found in publications, despite the abundant quantitative physical facts made available to us by the radiation physicists.[1,6,7,11,16,28,29,30,33]

The wider use and availability of the roentgen-ray generator and gamma-ray supervoltage equipment increase the need for knowledge of those factors which affect the design and performance of therapy machines in everyday practice. Therapy units that emit high energy gamma rays from cobalt 60 or cesium 137 sources should be designated as orthovoltage[34] if their design deviates from that of supervoltage equipment[6,24,33] which possesses skin sparing characteristics. These design deficiencies can be recognized and corrected.[9,31]

REVIEW OF THE LITERATURE

Failla, Twombly, and Marinelli[16] in 1937 recognized that electron contamination of the air volume between the diaphragm system and the skin in supervoltage roentgen-ray therapy increased the superficial skin dose. They reasoned that, although superficial skin dose might be reduced by means of electron filtration, the tolerance of subcutaneous tissues might still become the limiting factor in higher dosage administration.

Quimby's[28] 1939 review of tissue dosage measurement emphasized the problem of tangential irradiation. There is no adequate

* From the Radiation Therapy Department, St. Luke's Hospital, New York. Presented at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960. Also presented as a scientific exhibit at the Sixty-first Annual Meeting of the American Roentgen Ray Society, Atlantic City, New Jersey, September 27–30, 1960 and at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, December 4–9, 1960.

measuring instrument for this troublesome factor in supervoltage irradiation. In the same paper Quimby states that the "tissue dose for tangential irradiations can not be properly obtained from isodose charts made with the beam of radiation entering the body at right angles, nor can the exit dose be obtained from such charts." She suggests that "although the discussion of tissue dosage was based entirely on the basis of physical measurements, it must not be lost sight of that biological questions are also exceedingly important." This is especially so when considering the variation of skin reactions based purely on anatomic site, tissue texture and skin sensitivities.[3]

Witwer and Leucutia[36] in 1940 evaluated the late sequelae of varying voltages on the skin. On the basis of limited experience with 600 kv. roentgen-ray therapy they concluded that "supervoltage roentgen therapy permits irradiation with the least damage to the skin, and therefore one may surmise that the danger of late sequelae may be entirely dismissed." This supposition did not refer to "heroic forms of protracted irradiation in which excessive cumulative doses are used."

Dresser, Rude, and Cosman[13] in 1940 evaluated the difference between 200 kv. and supervoltage one million volt therapy and concluded that with supervoltage irradiation not only were the immediate superficial reactions less intense but late skin damage in a two year experience had been entirely absent. They did remark, however, that a few cases developed "stiff erythemas," and they attributed the reaction largely to the exit dose.

In 1940, Stone and Robinson[32] compared the production of a similar skin reaction in the same patient induced by 200 kv. and 1,000 kv. radiations. To them, the important consideration was the reaction, not the number of roentgens measured. Thus, if biologically equivalent reactions are obtained from two different energies, the doses should be considered equivalent despite a numerical difference in roentgens measured. A dose, for Stone and Robinson, is the total skin dose, or the sum of "r on skin" ("r in air" plus backscatter) plus the exit dose. They hypothesized that, in producing a particular skin reaction, treatment by 1,000 kv. radiation may involve more roentgens as measured in air or by total skin dose than from 200 kv. radiation, but the doses would be considered equivalent. In fact, they concluded that, "allowing for biological inaccuracies, to produce similar skin reaction with these two qualities of radiation requires about 25 percent more total skin dose of the 1,000 KV. rays." Conversely, they pointed out that the same number of "r in air" from the two types of apparatus would result in less skin reaction from the 1,000 kv. rays than from the 200 kv. rays. The study of Stone and Robinson loses some value, however, since they used pressure cones with both the 200 and 1,000 kv. machines. These introduced effects on the skin due to pressure and electron contamination of unknown magnitude.

Trump and Cloud[33] in 1943 discussed the progressive movement of maximum ionization below the surface of the skin as the voltage increases, and they emphasized that the subcutaneous effect was already considerable for 1,000 kv. They stated that "the subcutaneous dose of maximum intensity should be taken as the measure of incident dose." The need for the use of sufficient air wall material overlying the Victoreen thimble chamber, to ensure measuring maximum ionization, is made clear.

In the same year, Dresser[12] discussed the bolus effect of low density material placed on the patient's skin. If the material is of sufficient thickness, *e.g.*, 5 mm. for 3,000 kv. roentgen rays, maximum ionization occurs directly on the skin. This effect, although generally to be avoided, can be used to advantage where the skin may be, or is, invaded by tumor.

Holmes and Schulz,[23] in 1946, reported on the use of 1,200 kv., Van de Graaff generated roentgen rays. They reaffirmed the com-

monly held viewpoint that supervoltage radiation was less likely to induce serious skin damage. Air doses, however, rather than total superficial skin or maximum subcutaneous doses per field were measured. Administering 6,000 r measured in air to single fields in head and neck cases, they observed that reactions were confined to the treated site of the neck and they reported no exit dose reactions.

In 1950, an additional basic article appeared by Murphy and Reinhard,[27] attempting to compare orthovoltage and supervoltage skin reactions. In their paper, an approach similar to that of Stone and Robinson[32] was used in that they directed 200 and 1,000 kv. roentgen rays to adjacent skin areas in the same patient but it differed in that they gave the same total skin dose per field (entry dose plus exit dose) each day, as well as for the total course and in the same over-all time. A total of 19 cases was included in the study. Thirteen patients, each treated simultaneously with both modalities, exhibited the same immediate skin reactions on the last day of treatment; in 3 cases the reaction was greater on the side treated with 1,000 kv., while in the other 3 cases the side treated with 200 kv. reacted more intensely. At the final observation four months later, sequelae were equal for the 200 and 1,000 kv. therapy in each of 10 patients, greater for the 1,000 kv. in 1 case and more pronounced for the 200 kv. in each of 7 other cases. They generally concluded that, in the same patient and for the same skin dose, the immediate reactions are equal for 200 and 1,000 kv. roentgen rays.

In 1952, Dixon, Garrett and Morrison[11] reported complete data on the Eldorado teletherapy Co^{60} unit. (The same unit is used at St. Luke's Hospital, New York.) The most important facts they presented in reference to this supervoltage gamma ray equipment were the optimal source diaphragm distance and the optimal diaphragm skin distance. Both these factors give minimal penumbra and minimal electron contamination of the beam with maximum depth dose measurements. The supervoltage beam thereby produced is equivalent to that of a 3,000 kv. Van de Graff generator.

Miller[26] published depth dose measurements for a 2,000 kv. generator and showed that the dose delivered at a depth of 10 to 15 cm. is about ten per cent less than the dose delivered with cobalt 60 for the same maximum dose delivered in the skin.

Evans *et al.*[14] commented in 1954 on the Eldorado unit. They warned against the use of both closed- and open-end plastic applicators as they contribute electron contamination to the skin surface.

At St. Luke's Hospital, New York, the closed-end applicator on the Eldorado unit has never been employed.

Fried *et al.*[19] continued to use the Eldorado's closed-end applicator and resorted to rotational therapy to minimize skin reactions.

Haas, Harvey, and Laughlin[22] refer to the difference in average specific ionization as the important factor in 200 kv. versus higher kilovoltage skin effects.

Richardson, Kerman, and Brucer[30] in 1954 presented their evaluation of the effects of source skin distance, field size, cone inner lining and electron filters on the skin dose. They commented that for the same energy source, although the results should be similar, the actual measurements will vary with the design of the unit and the range of cone to skin distances.

The effect of closed-end applicators on the skin in supervoltage gamma therapy was presented in a paper published in 1954 by Burkell *et al.*[9] The skin reactions for the same field under open and closed parts of the applicator are shown in Kodachrome views. They observed that the skin reactions without closed-end applicators had been, in general, less pronounced than would have been expected with 200 kv. therapy. However, they included a photograph of a breast cancer patient who developed a moist skin reaction and deep pigmentation after a 4,000 r tumor dose administered in three weeks—a reaction

which can be considered severe even for 200 kv. therapy.

Friedman, Dresser, and Hine[20] in an article on 2,000 kv. roentgen-ray therapy also commented on the effects on the skin dose of target skin distance, electron emission from the collimating device and field size. They reported that with 8,000 r maximum skin dose delivered through a single portal, the only early skin reaction was a deceptively mild first degree erythema which healed rapidly. They did mention (without case presentation) that after using this dosage over a period of time severe radiofibrotic and radionecrotic effects will manifest themselves.

Fletcher *et al.*[17,18] pointed out in 1956 that, as with cobalt 60, the same optimal collimator-skin distance of 20 cm. also applies to a 2,000 kv. generator.[26] They cautioned, as others have, that subcutaneous fibrosis may occur. They also emphasized that the skin reaction on the exit side is as great as on the entry side and reported that, when using shorter collimator-skin distances without electron filters, moist desquamation had been observed.

Severe necrotizing skin reactions resulting from the use of cobalt 60 therapy machines with short collimator-skin distances are vividly demonstrated in a paper by Simon, Silverstone, and Gutman,[31] published in 1958, with their evaluation of the effectiveness of electron filters of different materials.

Burkell and Watson[8] in 1956 also pointed out the importance of eliminating closed-end applicators and avoiding the use of a bolus on the skin, if skin sparing is desired.

Baily and Beyer,[1,2] in 1957 and 1958, investigated the problems of surface and exit dose. They showed the significant variation of air dose rate and surface dose as a function of field size.

In 1959, Braestrup[6] presented the physical and Guttmann[21] presented the clinical advantages and limitations of cobalt 60 teletherapy. These two excellent papers give the essence of the factors which govern supervoltage gamma ray therapy. The authors also give the characteristics of units that have a short source-skin distance and short diaphragm distance. Except for the discussion by these authors on the influence of source size, all the other factors presented by them would apply equally as well to supervoltage roentgen-ray generators.

MATERIAL

Twenty-three patients, 19 white, 4 Negro, with skin and subcutaneous reactions are reported in this paper. The skin changes are illustrative of the full range that may be met with in supervoltage therapy.

Between 1955 and 1959, 700 malignant cases were treated on the Eldorado telecobalt unit at St. Luke's Hospital, New York. Of these, 160 (22.8 per cent) showed some degree of integumental reaction. Included in the 160 cases are the 23 cases presented in this paper. Additionally, 2 patients (J.W. and J.C.) treated at Memorial Hospital, New York, are mentioned in the text with the kind permission of Dr. Ralph Phillips. One of us (L.L.) while at that institution was privileged to assist in the treatment of these 2 patients and at that time became interested in supervoltage skin reactions.

IRRADIATION FACTORS

The St. Luke's Hospital Eldorado telecobalt unit conforms in design and performance to that described by Dixon *et al.*[11] Since the time of its original installation in 1954, and also at the present time, this unit has contained a cobalt 60 source 3 cm. in diameter with a half value layer of 1.1 cm. Pb.

Initially, the output at 80 cm. source skin distance was 44.5 r/min.; with the second source replacement made in December, 1957, the output was 57.6 r/min. at 80 cm. Monthly output corrections for decay are routinely made. The unit has been consistently operated with a source-diaphragm distance of 59 cm., a diaphragm-skin distance of 21 cm. and a source-skin distance of 80 cm. or 100 cm. for nonrota-

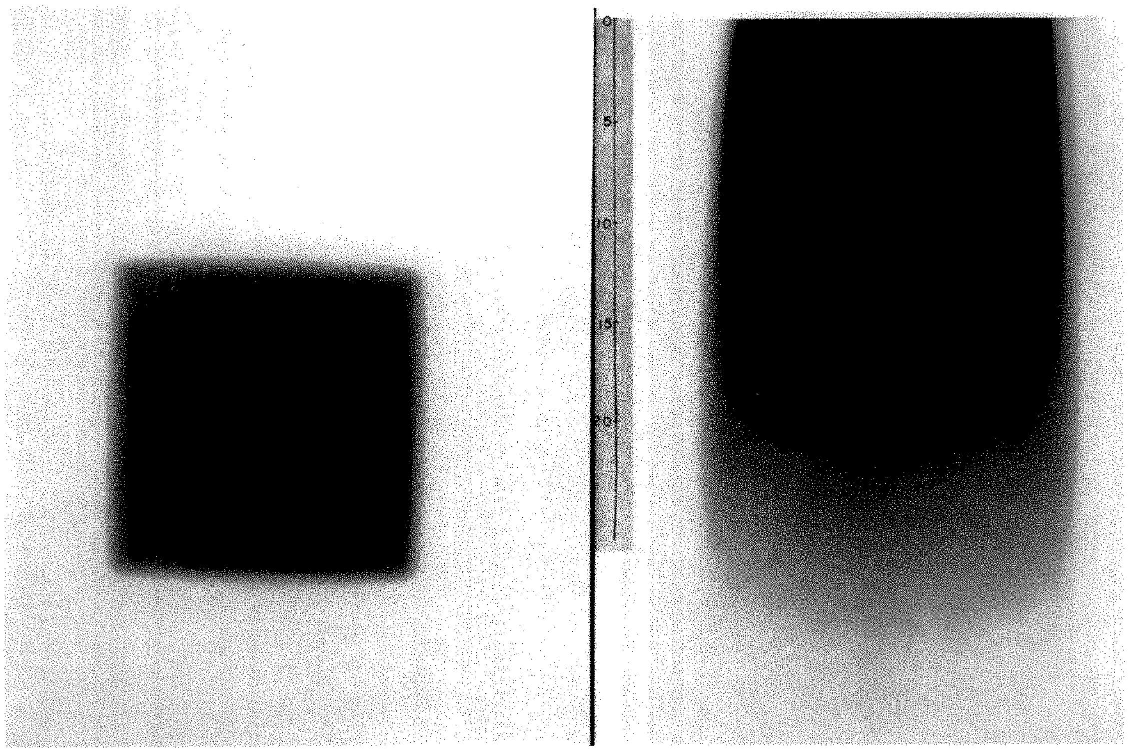

Fig. 1. Industrial type AA x-ray film exposed to a cobalt 60 beam in a large pressdwood phantom (SSD, 80 cm.; DSD, 21 cm.; FS, 15×15 cm.; source diameter, 3 cm.). The film is perpendicular to the beam axis (left) and parallel to the beam axis (right).

tional therapy. A light localizer with the mirror located near the source and fine wire cross hairs at the open face of the diaphragm aid in field centering. An open-end shaping platform with lead bars supported on the head of the machine outside of the field of irradiation is part of our auxiliary equipment but it was not employed in any of the cases reported in this paper.

All physical data for our unit relating to optimum diaphragm-skin distance, central axis depth doses, air dose rates, and surface and maximum dose rates for different field sizes at 80 and 100 cm. source distances were measured by one of us (N.M.). These determinations with slight variations confirm the results of Dixon *et al.*[11] As listed in Table II, the air dose rate as a function of field size varies significantly because of electron scatter from the variable diaphragm. The air dose rate increases to a maximum with our unit when a 15×15 cm. field size is attained, decreasing somewhat to a plateau thereafter. Enlarging the field size beyond 15×15 cm. apparently does not further increase the number of secondary electrons sufficiently energetic to be collected by an appropriate lucite capped Victoreen or Bomke ionization chamber. Similarly, the maximum dose and surface dose* vary with the field size.

The photographs in Figure 1 are of industrial type AA x-ray film, exposed in a large pressdwood phantom to the Eldorado telecobalt beam. We used a 15×15 cm. field to emphasize the uniformity of density across even a large field and the minimal penumbra present. With a densitometer we determined that the penumbra for such a large field is less than 1 cm. and for smaller fields is negligible. The latter was confirmed to our satisfaction clinically in cases where treatment was directed to the maxillary sinus in close proximity to the eye; sharp

* Surface skin dose refers to extrapolated values to zero thickness.

TABLE I

FACTORS INFLUENCING SKIN REACTIONS AND THE DIRECTION OF THEIR EFFECTS ON SKIN REACTIONS

I. Physical	Physical (Continued)	II. Time-Dose Relationship	III. Skin	IV. Superimposed
A. Energy of Beam Medium ↑ High ↓ B. Diameter of Source Small ↓ Large ↑ C. Equipment Design 1. Target or Source Skin Distance Short ↑ Long ↓ 2. Collimator (diaphragm) a. Lining High Atomic Number ↑ Medium Atomic Number ↓ b. Diaphragm Skin Distance Short ↑ Long ↓ c. Cone (end) Closed ↑ Opened ↓ 3. Shaping Platforms ↑ D. Bolus Tissue or Tissue Equivalent ↑ Density >Tissue ↑ ↑	E. Scatter Effects 1. Entry Underlying Bone ↑ 2. Exit a. Table Metal ↑ ↑ Foam Rubber ↑ b. Table Dimension Narrow ↑ Wide ↑ ↑ F. Exit Dose Low ↑ High ↑ ↑ G. Angle of Incidence on Skin Surfaces Direct ↓ Tangential ↑ H. Treatment Planning Rotational ↓ Multiportal ↓ Parallel Opposing ↑ Single ↑ ↑ I. Field Size Small ↓ Medium ↑ ↑ Medium Large ↑	A. Total Daily Dose per Field (entry+exit) Low ↓ Medium ↓ ↑ High ↑ B. Total Number Treatments Many ↓ Few ↑ C. Over-all Time Short ↑ Long ↓ D. Total Accumulative Dose per Field (entry+exit) Low ↓ High ↑ E. High Dose Over Short Time ↑ F. High Dose Over Long Time ↑ ↓	A. Characteristics Vascularity ↑ Texture Fine ↑ Pigmentation ↓ Skin Thickness Thin ↑ Sulfur Content High ↑ Obesity ↑ B. Anatomic Site Scalp ↓ Neck ↓ Chest ↓ Abdomen (obese) ↑ Groin, Perineum, Axilla ↑ Extremities ↓ C. Skin Surface Flat ↓ Curved ↑ Tangential ↑ Intertriginous ↑	A. Prior Treatment Irradiation ↑ Surgery ↑ B. Wound or Skin Infections ↑ C. Applied Heat, Actinic Rays, and Chemicals ↑ D. Trauma ↑ E. Systemic Therapeutic Agents (actinomycin D) ↑ F. Heightened Metabolic States ↑ G. Gaseous Perfusions Oxygen ↑ Nitrogen ↓ H. Environmental Temperature High ↑ Low ↓ I. Anemia

demarcations of skin reactions in these planned treatment fields are always observable. Depending upon the diaphragm system and source size of a given supervoltage unit, the maximum and skin doses for a given tumor dose will vary according to the design. Values could be greater, less than or the same as with our unit.

The last three columns of Table II, list the delivered total skin and maximum dose (entry+exit) per field and the total tumor dose attained in each case. The skin-tumor dose relationship remained favorable in every instance, even though parallel opposing fields were used. On the other hand, the maximum (0.5 cm. depth) dose exceeded or was equal to the tumor dose in all cases but 2, which we interpret as an unfavorable subcutaneous tissue-tumor dose relationship. No tumor dose administered in these cases exceeded 6,000 r.

Skin reactions induced by supervoltage radiation must be viewed in terms of the many factors listed in Table I.

Given the operative variables plus the possibility of their effects being additive, it would appear virtually impossible to avoid at least a minimal skin reaction, yet not all of our patients developed skin reactions. We believe, therefore, that our over-all incidence of 22.8 per cent for all gradations of skin reactions is realistic and valid.

If we are cognizant of even a few factors (such as electron contamination arising from short diaphragm-skin distance[30] and poor cone design[31] as well as the effect of

bolus material on the skin dose[22]), skin reactions may be kept to a minimum. The additive effects on the skin, however, of such adverse factors as an unfavorable time-dose relationship, skin site and physiology, as well as the other superimposed influences listed in Table I, may well outweigh any attempts we make at improving the physical features of a supervoltage unit.

Table II contains information routinely entered on our radiation therapy charts. The complete data include: half-value layer, source-skin distance, diaphragm-skin distance, applicator design, presence or absence of bolus material, field size, field arrangement, total individual number of treatments, daily and total cumulative skin and maximum doses (entry + exit), and the over-all time of the course of treatment.

Table II also shows the significant entry percentage skin doses, ranging from 35 per cent for smaller fields to 70 per cent of the maximum dose for fields of 300 cm.^{2} or more. If parallel opposing fields are used, as they were in all our patients but 1, and if the interfield separation is small, as exemplified in head and neck cases, the percentage exit dose may be higher than the entry dose with exit dose values as high as 53 per cent.

The column headings in Table II designating "total daily skin and total daily maximum" doses have been devised by us to emphasize the entry and exit dose contribution per field to the skin and subcutaneous tissues from opposing fields treated alternately in each twenty-four hour period.

Field sizes varied depending upon the extent of the tumor and anatomic site. Small fields (30–150 cm.^{2}) were used in 6 patients; medium fields (150–300 cm.^{2}) in 10 patients; and large fields (300–420 cm.^{2}) in 7 patients.

The over-all time of the course of treatment expressed in weeks rather than days was: three weeks in 5 patients, four to seven weeks in 17 patients, and eight to nine weeks in 2 patients. (One patient had two courses of treatment separated by a three year interval.)

REACTIONS

Skin reactions induced by supervoltage radiation as reported in this paper fall into two main categories: (1) those induced without bolus material intervening in the beam and without an unusual time dose relationship; and (2) those induced with bolus material intervening in the beam or with an unusual time dose relationship. These two categories are each further subdivided according to the type of reaction and the topography of the skin surface, *i.e.*, flat, curved (tangential), or intertriginous.

The first category contains 21 patients with the following number and types of reactions: erythema—flat surface, 3; follicular erythema—flat surface, 1; dry desquamation and tanning—flat surface, 2 (Fig. 2); moist desquamation—flat surface, 1; moist desquamation—intertriginous surface, 4 (Fig. 3); dry desquamation—tangential surface, 2 (Fig. 4); dry desquamation and late subcutaneous fibrosis—tangential surface, 1 (Fig. 5); and subcutaneous fibrosis—flat surface, 7 (Fig. 6, *A* and *B*).

One of the 4 patients with moist desquamation on an intertriginous surface (patient J.C.*) is not listed in our tables. Treatment factors were as follows: theratron Co^{60} machine, 360° horizontal rotation and an 8×12 cm. field for an over-all time of forty-two days and a total tumor dose of 6,000 r. Severe moist desquamation began with a 4,000 r tumor dose accumulated in thirty days.

The second main category contains 4 patients with the following reactions: follicular tanning—flat surface, 1 (patient R.N., Table II); moist desquamation—intertriginous surface, 1 (patient F.P., Table II); moist desquamation—bolus, 2 (patient W.St.C., Table II and Dr. Phillips' patient, J.W.).

Since patient J.W.* is not listed in our

* These patients were treated at Memorial Hospital, New York, and are included with the permission of Dr. Ralph Phillips.

TABLE II

FACTORS OF COBALT 60 IRRADIATION

(SOURCE-SKIN DISTANCE—80.0 cm., DIAPHRAGM-SKIN DISTANCE—21.0 cm., SOURCE DIAMETER—3.0 cm.)

Site	Patient	Over-all Time (days)	Field Size (cm.)	Fields	Air Dose Rate (r/min.)	Skin Dose (per cent)	Max. Dose (per cent)	Exit Dose (per cent)	Daily Skin Dose per Field			Daily Maximum Dose per Field*			Final Total Dose per Field (entry+exit)		Tumor Dose (r)
									Entry Dose (r)	Exit Dose (r)	Total Dose (r)	Entry Dose (r)	Exit Dose (r)	Total Dose (r)	Skin Dose (r)	Max. Dose (r)	
Head and Neck	W.M.	38	5×6	// opposed	43.3	35.0	100	51.5	106	157	263	304	156	460	3,400	6,000	6,000
	J.Mc.	42	5×6	// opposed	42.6	35.0	100	52.7	91	137	228	260	137	397	4,200	6,000	6,000
	L.C.	41	5×6	// opposed	47.2	35.0	100	51.0	91	133	168	261	133	394	3,400	6,000	6,000
	G.K.	43	5×6	// opposed	42.6	35.0	100	52.5	91	137	228	262	137	399	4,300	6,200	6,000
Supraclavicular	J.M.	43	11×11	// opposed	46.5	50.0	104	40.0	148	118	266	296	118	414	3,900	5,900	4,600
	A.M.	42	15×15	// opposed	47.0	63.0	105	50.0	159	133	292	266	133	399	4,400	6,000	6,000
	M.P.	22	10×20	// opposed	46.7	62.0	102	42.0	220	150	370	350	124	474	2,700	3,800	3,700
	C.O.	35	12×15	Single, direct	53.2	60.0	104	40.0	153	102	355	255	—	255	3,800	6,400	5,000
Chest-Axilla	H.P.	44	17×22	// opposed	50.0	70.0	106	27.0	240	93	333	344	93	437	5,000	6,600	6,000
	P.G.	46	15×26	// opposed	44.4	70.0	106	25.0	250	96	346	385	96	481	5,200	6,200	6,000
Breast	W.St.C.	27	12×18	// opposed, tangential, bolus	48.5	64.0	105	22.0	256	88	344	400	88	488	3,400	4,800	4,000
	A.K.	28	13×17	// opposed, tangential, no bolus	54.2	64.0	104	30.0	220	100	320	344	103	447	3,200	4,500	4,000
Abdomen	H.A.	35	15×15	// opposed	51.0	64.0	102	15.0	332	64	396	520	64	584	3,600	5,900	4,000
Pelvis	F.P.	19	20×18	// opposed	45.0	70.0	106	15.0	500	105	605	700	105	805	3,900	5,300	4,100
	A.N.	1. 24 (3 yr. interval)	12×12	Four // opposed	53.0	51.0	102	10.0	195	40	235	379	38	407	2,000 2,500	3,900 5,000	4,700 4,300
		2. 31	9×12	Four // opposed	55.5	55.0	103	10.0	165	38	203	383	38	421	4,500	8,900	9,000
	I.S.	60	14×15	Four // opposed	55.6	63.0	105	20.0	350	110	460	550	110	660	3,500	5,300	6,000

Site	Patient	Over-all Time (days)	Field Size (cm.)	Fields	Air Dose Rate (r/min.)	Skin Dose (per cent)	Max. Dose (per cent)	Exit Dose (per cent)	Daily Skin Dose per Field: Entry Dose (r)	Daily Skin Dose per Field: Exit Dose (r)	Daily Skin Dose per Field: Total Dose (r)	Daily Maximum Dose per Field*: Entry Dose (r)	Daily Maximum Dose per Field*: Exit Dose (r)	Daily Maximum Dose per Field*: Total Dose (r)	Final Total Dose per Field (entry+exit): Skin Dose (r)	Final Total Dose per Field (entry+exit): Max. Dose (r)	Tumor Dose (r)
	E.D.	37	18×15	// opposed	51.3	65.0	105	30.0	234	108	342	360	108	468	4,300	5,600	5,000
	G.K.	39	21×15	// opposed	46.0	68.0	106	30.0	198	90	288	302	90	392	4,100	5,600	5,000
	R.N.	19	14×13	// opposed	45.5	60.0	105	35.0	400	140	540	600	175	775	3,000	4,300	4,000
	L.F.	40	22×19	// opposed	45.0	70.0	106	20.0	296	85	381	424	85	509	4,000	5,600	4,300
	R.B.	30	20×20	// opposed	48.5	70.0	106	30.0	240	115	355	345	104	449	3,500	4,000	4,0000
	J.M.	55	22×14	// opposed	49.5	70.0	104	25.0	264	95	359	378	95	473	5,000	6,100	6,000
Hip	L.G.	23	11×15	// opposed	45.8	59.0	104	28.0	260	121	381	440	121	561	2,200	4,800	4,000

* At 0.5 cm. depth.

FIG. 2. Patient P.G. Photograph taken fourteen days after the last treatment shows marked tanning and marked dry desquamation. A superficial skin dose (entry+exit) of 5,200 r was administered through 15×[illegible] cm. parallel opposing fields in an over-all time of forty-six days. No bolus was used. This is an example of a reaction on a flat surface.

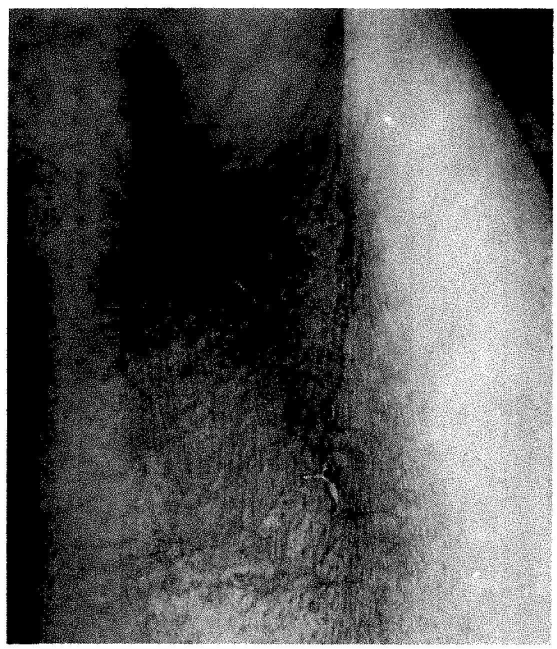

FIG. 3. Patient H.P. Photograph taken at the end of therapy shows marked erythema and moist desquamation in the right axilla. A superficial skin dose (entry+exit) of 5,000 r was administered through 17×22 cm. parallel opposing fields in an over-all time of forty-four days. No bolus was used. This is an example of an intertriginous reaction.

FIG. 4. Patient C.O. Photograph taken four days after the end of therapy shows marked dry desquamation and tanning. This view shows the exit side of a single 12×15 cm. anterior supraclavicular-axillary field. Superficial skin dose (entry) 3,800 r, exit dose (without backscatter) 2,500 r, maximum dose 6,400 r. The dose was delivered in an over-all time of thirty-five days in 25 individual treatments. This is an example of tangential skin and exit dose effects.

FIG. 5. Patient A.K. Photograph taken eight months after completion of therapy shows marked subcutaneous fibrosis following medial and lateral parallel opposing tangential irradiation of primary inoperable breast cancer. No bolus was used. A skin dose (entry+exit) of 3,200 r and a maximum dose (entry+exit) of 4,500 r were delivered through 13×17 cm. fields in an over-all time of twenty-eight days. Erythema was present at the completion of the course and there was marked dry desquamation three months later. The adjacent rectangular reaction was secondary to 140 kv. therapy. This is an example of subcutaneous fibrosis following tangential irradiation.

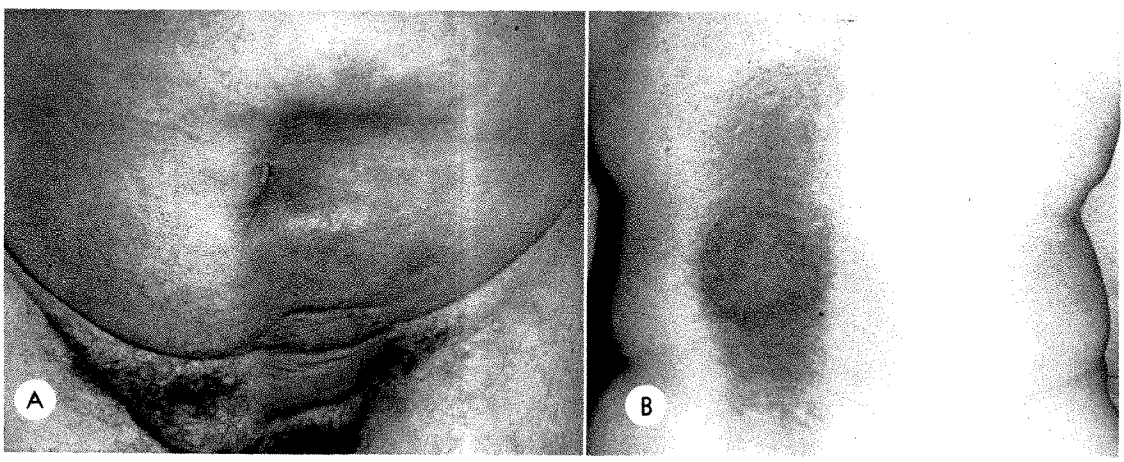

FIG. 6. (*A*) Patient H.A. Photograph taken thirty-three months after the last treatment shows very severe, retracted, pigmented, brawny-hard subcutaneous fibrosis of the anterior abdominal-pelvic wall. A maximum subcutaneous dose (entry+exit) of 5,[illegible]00 r was delivered through upper and lower 15×15 cm. parallel opposing fields (superficial skin dose 3,[illegible]00 r) in an over-all time of thirty-five days in 25 individual treatments. Reaction occurred only in the more midline portions of the field irradiated. This was first observed three and one-half months after the completion of therapy. (*B*) Same as *A* showing subcutaneous fibrosis over the posterior portals. The reaction in this patient is an example of severe subcutaneous fibrosis.

Table III

ANALYSIS OF SKIN AND SUBCUTANEOUS REACTIONS INDUCED BY SUPERVOLTAGE (COBALT 60) IRRADIATION

		Early Reactions						Late Reactions		Total Dose per Field (entry +exit)		
								Subcutaneous Fibrosis				
Site	Patient	Erythema	Erythema and Tanning	Tanning	Desquamation and Tanning	Moist Desquamation—Flat Surface	Moist Desquamation—Intertriginous Surface	Without Inflammation	With Inflammation	Skin Dose (r)	Subcutaneous Dose (r)	Remarks
Head and Neck	W.M.	++				++				3,400	6,000	
	J.MC.	++								4,200	6,000	
	L.C.	+								3,400	6,000	
	G.K.	+								4,300	6,200	
Supra-clavicular	J.M.		++		++					3,900	6,000	Tangential effects
	A.M.			++	+++					4,400	6,000	
	M.P.							—		2,700	3,800	
	C.O.	+			+++					3,800	6,400	Tangential effects
Chest	H.P.	+	++				++			5,000	6,600	Chest wall, axilla
	P.G.		+		+++					5,200	6,200	
Breast	W.St.C.	+					+++			3,400	4,800	Bolus
	A.K.	+			++			−++		3,200	4,500	No bolus
Abdomen	H.A.								++++	3,600	5,900	Very obese
Pelvis	F.P.	+++					+++			3,900	5,300	
	A.N.								++	4,500	8,900	2 courses, 3-yr. interval
	I.S.						++		+++	3,500	5,300	Obese
	E.D.			++	++			−++		4,300	5,900	Thin abdomen
	G.K.	+			++		+			4,100	5,600	
	R.N.		+++							3,000	4,300	
	L.F.	++					++			4,000	5,600	Very obese
	R.B.	+						++		3,500	4,000	
	J.M.	++						+++		5,000	6,000	
Extremities	L.G.	+++								2,200	4,800	Follicular reaction

Reactions: 18 erythema (with or without tanning); 9 tanning (with or without desquamation); 7 moist desquamations; 8 subcutaneous fibrosis.

tables, a brief résumé of the case follows: Treatment was with a 1,000 kv. General Electric Resonant transformer with a focal skin distance of 70 cm., half value layer of 3.7 mm. Pb, parallel opposing 18×12 cm. fields, with the beam passing through a 1.5 cm. thick, circular plaster cast. Twenty-eight days after initiation of therapy, a window was made in the cast overlying the treatment field exposing a most intense, violaceous, vesicular, moist desquamation. The Victoreen and Baldwin-Farmer chamber readings indicated a superficial skin dose in the presence of a plaster bolus of 4,400 r (entry dose plus exit dose) delivered in an over-all time of twenty-eight days. Dr. Arvin Glicksman (Memorial Hospital, New York) was responsible for the triiodothyronine therapy that was effective in inducing rapid skin healing in this patient.

Table III lists the intensity of each type of reaction. Early reactions refer to those evident during therapy and in the immediate post-treatment interval. Late reactions refer to those occurring at least one month after treatment. Patients have demonstrated either a single isolated reaction or a sequence of multiple reactions that proceeded to healing.

In the 23 patients listed, 18 erythematous reactions (in 17 patients) were observed, 14 of which were erythema alone,

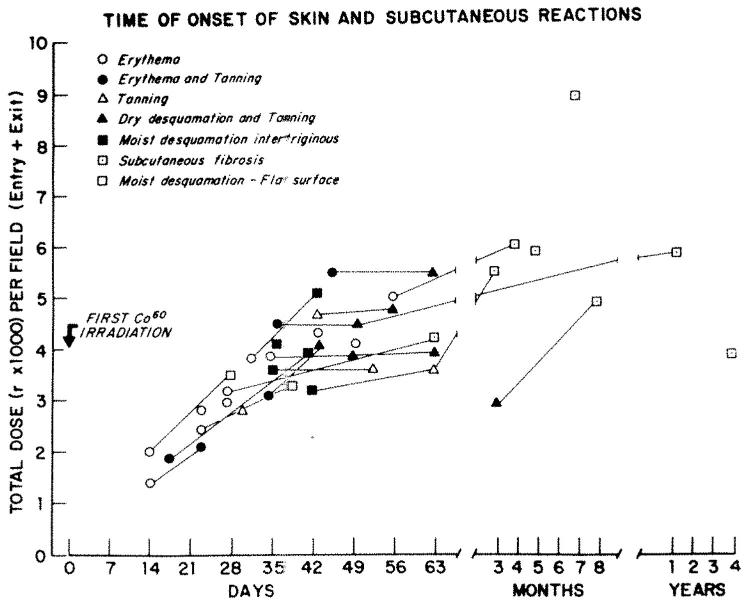

Fig. 7. Graphs showing the time of onset of skin and subcutaneous reactions.

with tanning occurring simultaneously in 4. There were 9 tanning reactions; 7 of these were accompanied by dry desquamation. Only 1 instance of moist desquamation on a flat surface was observed; a bolus was not used on this patient. Six instances of moist desquamation in intertriginous areas were recorded.

There were 8 late subcutaneous fibrotic reactions, 6 in the abdominal-pelvic or lumbar area and 1 each in the breast and sternal areas. Of the 8 subcutaneous reactions, 3 were accompanied by intense inflammation (patient I.S. had a superimposed low grade abdominal wound infection).

In evaluating supervoltage skin and subcutaneous reactions from the aspect of the anatomic site irradiated, our analysis reveals that 12 patients are in the head and neck, supraclavicular, chest, and breast groups; they demonstrated 20 early skin reactions and 2 late subcutaneous fibrotic reactions. The main features these cases had in common were curved skin surfaces, smaller interfield separation and, consequently, higher exit doses. In the 11 other patients where treatment was directed to the abdomen, pelvis, or extremities, 14 early skin reactions and 6 late subcutaneous fibrotic reactions were noted. All of these 11 patients were obese; they had healed or healing abdominal incisions; there were large interfield separations; and the treated skin surfaces were intertriginous.

Figure 7 shows the time of onset of various skin and subcutaneous reactions on three different time scales. The mildest skin reactions did not occur earlier than two weeks after the start of irradiation, appearing within a range of fourteen to fifty days. The majority of these first reactions became evident between twenty-one and forty-two days after the initiation of treatment. Erythema may be present as the earliest and only reaction (Fig. 7). Similarly, tanning, dry desquamation, moist intertriginous changes and subcutaneous fibrosis may appear without milder preceding reactions. The classic sequence of skin changes described for lower voltage therapy is not always evident in supervoltage therapy. Five of the 8 subcutaneous fibrotic reactions were accompanied only by erythema or were not preceded by any skin change at all.

Excluding subcutaneous reactions, the interval between the earliest skin reactions

and fully developed reactions was two to three weeks in most cases. The interval between the fully developed reaction and healing was generally two weeks. In 4 cases, however, complete healing required one to three months, calculated from the time of appearance of the maximum reaction. The total time interval, therefore, between the first appearance of the earliest reaction and final skin healing ranged between two and four months.

Subcutaneous fibrosis, measured from the time of the first treatment, developed in 1 case at two months, in 5 cases between two and seven months, and in 2 cases at one year and four years, respectively (Fig. 7).

The earliest reactions appeared at skin doses of 500 to 1,500 r below the final administered skin dose in 10 cases (approximately 40 per cent) of the total of 23 reported. In 6 cases (approximately 25 per cent of the 23 reported) the earliest reactions first appeared when the total skin dose (entry+exit) had been administered, becoming a fully developed reaction thereafter. Fully developed skin reactions in most patients first appeared only after the administration of the total skin dose (entry+exit).

Figures 7 and 8 are based on reactions induced by supervoltage radiation without the use of an intervening bolus (except case W.St.C., advanced breast cancer invading the axilla and skin of the breast) or an unusual time dose relationship (except cases R.N. and F.P.).

Figure 8 plots the final fully developed maximum skin and subcutaneous reactions relative to total skin and maximum dose (entry+exit) delivered and to field area in square centimeters. We were able to define three fairly distinct reaction groups in which a dose to field area relationship seems apparent.

For smaller fields (30–180 cm.^{2}), total skin doses (entry+exit) ranging between 3,500 r and 4,500 r generally may be given without a reaction greater than erythema and tanning. (Case W.M. is an exception, Table II.)

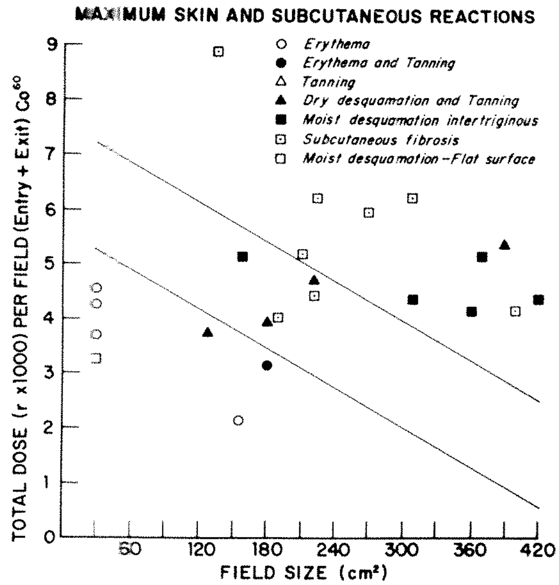

FIG. 8. Graphs showing maximum skin and subcutaneous reactions.

For moderately sized field areas (150–210 cm.^{2}), total doses (entry+exit) ranging between 3,800 r and 5,300 r delivered to abdominal-pelvic sites will result in more intense reactions, including some cases of subcutaneous fibrosis.

With larger field areas (230–420 cm.^{2}) and with total doses (entry+exit) ranging between 4,000 r and 6,500 r, a markedly increased incidence of more intense skin and subcutaneous fibrotic reactions can be expected, especially in the abdominal-inguinal-perineal intertriginous areas.

In 1 case subcutaneous fibrosis occurred four years after the first course of therapy and after an accumulated dose of 8,900 r, with an interval of three years between the two courses of therapy (case A.N., Table II).

We have observed no instance of an acute skin reaction failing to heal. Radiation ulceration or necrosis of the skin has not occurred in any of the 700 cases treated by us with telecobalt therapy.

Of the acute supervoltage skin reactions, intertriginous moist desquamation represents the greatest problem to the therapist. Particularly troublesome are reactions oc-

curring in the axillary, inguinal, perineal and perianal areas. This complication is painful and distressing to the patient. It may require discontinuance of therapy, preventing the delivery of a proper cancericidal dose. These intertriginous reactions are in no way limited to stationary field therapy. Some of the most intense and painful reactions have occurred during horizontal rotational therapy (Dr. Phillips' patient J.C.).

DISCUSSION

The mechanisms which may cause these intertriginous reactions are related to the physics of supervoltage ionizing radiation and the physiology of the intertriginous skin surfaces, especially in the inguinal-perineal area. One can readily observe in all patients an increased pigmentation in these areas, which suggests a unique physiology and perhaps an altered sulfur content. This pigmentation is intensified both with conventional and supervoltage roentgen rays so that the higher reactivity in these areas must be related to ionizing radiation, irrespective of quality. The increased ionization in skin surfaces, due to the tangential incidence of photons and the bolus effect of opposed skin surfaces, causes heightened reaction in these intertriginous zones, whereas the same calculated skin dose delivered to adjacent flat surfaces is not usually associated with a skin reaction.

In horizontal 360° rotational therapy this also happens. As an example, in patient J.C. the buttock skin hyper-reacted while the anterior suprapubic skin, although also reacting, was remarkably less affected. The treatment table on which the patient lay acted as a bolused surface so that during part of the rotation, when the photons were directed from underneath the table, electron equilibrium attained maximal value in the table thickness and continued thereafter onto the skin of the buttock.

One of us (L.L.), in 1956, suggested that of the two factors, bolus and tangential effects, the tangential incidence of photons was more significant in producing moist reactions in intertriginous zones, such as the inguinal-vulval-perineal areas. This was based on the observation that heightened erythemas occurred on the lateral chest wall without bolus, when the beam incidence was tangential to such a curved surface. In order to substantiate this observation, skin dose rates (Table IV) were measured with chambers placed at tangential and intertriginous perineal surfaces, with and without a bolus. These measurements corroborated the prediction that tangential skin surfaces would receive a lower dose rate if they were incorporated into a bolused volume. We recognized, however, that the increased softer scatter from the adjacent bolus might outweigh the apparent advantage of eliminating the additive dose resulting from maximum ionization building up in the superficial skin parallel to its surface, as the incident photons penetrate tangentially.

Subsequent to these measurements, all curved surfaces (axilla, chest wall and vulval-perineal area) were filled in with an appropriate number of bolus bags in patients under our care. As a general rule, at the present time we do not use a bolus in this fashion. We individualize, however, in the use of a bolus depending on the obesity, pigmentation and field placement. Routinely, we attempt by the use of proper pillow support to keep irradiated surfaces perpendicular to the incident beam.

Contrary to the report of Murphy and Reinhard,[27] we believe that, for the same total skin dose per field, delivered to the same anatomic site through the same field size and for the same time dose interval, supervoltage radiation induces substantially less reaction than conventional orthovoltage roentgen rays, despite the occurrence of severe intertriginous moist reactions and subcutaneous fibrosis.

The relative skin sparing of supervoltage radiation compared to 200 kv. roentgen rays is dramatically evident when large field therapy is employed. The most intense reaction observed by us on a flat surface

TABLE IV

SURFACE DOSE RATES

Tangential Surfaces	Modality	Field Size (cm.)	TSD or SSD (cm.)	Air Dose Rate (r/min.)	Type of Chamber Used	Readings (r/min.)		Calculated Dose (r/min.)	
						No Bolus	Bolus	No Bolus	Bolus
Lateral chest wall	1 mev.	22×23	100	43.5	Victoreen	43.5	37.7	41.5	39.5
Lateral breast	1 mev.	31×23	100	46.5	Victoreen	44.0	41.0	52.0	52.0
Perineum	Co^{60}	10×6.8	75	—	Victoreen	10.0	8.4	—	—
Lateral hip	Co^{60}	15×15	80	44.0	Bomke 4 mm. cap	33.6	25.2	34.8	23.0
					Bomke no cap	29.4	24.2		
Flat Surface									
Anterior thigh*	1 mev.	18×12	70	87.0	Victoreen	—	70.5	—	
					Baldwin-Farmer		71.3		80.9†

* Overlying plaster cast 1.5 cm. thick.
† Based on soft tissue bolus.

occurred in a patient (Case P.G., Table II and Fig. 2) in whom a total superficial skin dose of 5,200 r was delivered to a skin area of 390 cm.[2] over a usual time interval. His skin reacted with intense tanning and marked dry desquamation. Had this same dose been delivered to a similar area with 200 kv. roentgen rays, a most severe necrotizing moist desquamation would have resulted.

We urgently caution the reader against applying the dosage information and resulting skin reactions reported in this paper to therapy with cobalt 60, cesium 137, or other future gamma-ray units that are designed for short source-skin distances or short diaphragm- or cone-skin distances. This applies especially to units with cone ends closed with low atomic number material such as lucite. Severe reactions will occur even if cone ends are open unless appropriate electron filters are used.[31]

CONCLUSIONS

Supervoltage gamma and roentgen-ray radiations exert a skin sparing effect which is dependent, however, on a variety of factors. The most important are: (1) minimal electron contamination of the beam; (2) absence of bolus material overlying the skin; (3) total skin or subcutaneous doses not exceeding the tolerance of these tissues; (4) clinically acceptable time-dose intervals; and (5) favorable anatomic site.

If these optimal conditions prevail, all factors being equal, supervoltage radiation induces considerably less skin reactions, roentgen for roentgen, than conventional kilovoltage roentgen rays.

Despite the skin sparing advantages of supervoltage radiations, observable skin reactions are induced in about one quarter of all patients who undergo therapy for deep-seated malignancies and in whom parallel opposing fields are used. Approximately 10 per cent of these patients (less than 2.0 per cent of the total number treated) demonstrate significant degrees of early erythema, tanning, tanning and desquamation, and moist desquamation, especially in intertriginous zones. Subcutaneous fibrosis occurs in 5 per cent of all patients reacting (1 per cent of the total number treated).

Severe moist reactions occurring in the vulval-perineal area are not confined to

stationary therapy alone but also occur with horizontal rotational therapy.

In supervoltage therapy, skin reactions are less dependent upon field size for the same delivered dose than in 200 kv. therapy. It is not unusual in supervoltage therapy for large skin areas treated with higher total doses to react less than smaller fields to which lower total doses have been administered. Anatomic site, more often than not, determines the degree of skin reaction rather than the field area or total dose.

Supervoltage radiation induced reactions differ from those seen with conventional or lower voltage therapy in that the classic sequence of changes[3] is not always manifest; *i.e.*, erythema may or may not appear first, if at all. More often, erythema and tanning occur simultaneously, thus making it impossible to distinguish at the onset between the two; tanning or moist desquamation is frequently seen as the initial reaction.

Subcutaneous fibrosis is peculiar to supervoltage therapy and, if it occurs, it almost always follows abdominal or pelvic irradiation. This happens more frequently in obese patients but occasionally in thin patients (Case E.D., Table II). It rarely occurs if the total maximum subcutaneous dose is less than 5,000 r (Case R.B., Table II).

SUMMARY

1. Supervoltage irradiation is skin sparing if certain conditions are met. Not all high energy gamma ray units conform to supervoltage design and may be better designated as the orthovoltage type, which can induce skin reactions similar to those in 200 kv. therapy.

2. Significant skin and subcutaneous reactions are induced by supervoltage irradiation even if optimal conditions prevail, the anatomic skin site perhaps being the most important factor, other things being equal.

3. Supervoltage radiation induced skin reactions may not follow the sequence of events described for lower voltage radiation. Erythema frequently does not occur or, if present, it merges imperceptibly with a tanning reaction.

4. Measures that can be taken to limit the incidence and intensity of supervoltage induced skin reactions are derived from knowledge and manipulation of the various factors listed in Table I.

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We wish to thank Mr. Richard Nelson of the Department of Physics, Treatment Planning Section, Memorial Hospital, New York for his cooperation in carrying out (in 1956) the surface dose rate measurements on both the 1,000 kv. machine and the theratron cobalt unit (SSD-75 cm.) recorded in Table IV.

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ABDOMINAL IRRADIATION AND THE THYMUS OF THE ADULT RAT: THE RELATIVE IMPORTANCE OF THE ADRENAL GLANDS AND OF SCATTERED RADIATION*

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IT IS a matter of fundamental importance to determine how much of the effects of irradiating the animal are due to direct cellular damage and how much to the liberation into the blood stream of physiologically or pharmacologically active substances. The most direct way of proving the existence of such substances would be to demonstrate radiation effects in unirradiated tissues, either by cross circulation experiments or by localized, part body irradiation with adequate biologic controls for the unavoidable effects of scatter on the shielded tissues.

Cross circulation experiments in the cat failed to reveal any such "indirect" effect of radiation on hematopoiesis.[8] However, experiments in which the thymus, spleen and lymph nodes were examined after abdominal irradiation of intact and adrenalectomized rats were interpreted as showing that indirect effects of irradiation do occur, at any rate after large doses, and are mediated via the adrenal gland.[9,12] These important conclusions have been generally accepted and often quoted, even though there appears to be a hidden discrepancy in the original reports.

Leblond and Segal,[9] in 1942, published the combined results of two series of experiments, the first having been reported earlier.[12] By analyzing the two reports, it should be possible to deduce the results of their second series of experiments and this has been done in Table I. It can be seen that there is an important difference between the results of the first and second series. In the first series, adrenalectomy indeed abolished the effect of abdominal irradiation on the weight of the thymus but, in the second series, adrenalectomy seemed to make very much less difference; in the adrenalectomized rats, the weight of the thymus was reduced by 60 per cent compared to 72 per cent in the intact rats.

It would appear, therefore, that the role of the adrenal glands in the effect on the thymus gland of local abdominal irradiation needs re-examination, especially as the general question of the degree to which the adrenal glands participate in the reactions of the body after experimental whole body irradiation is a matter of lively controversy.[1,2,5,11]

In the present experiments, large volumes of tissue were irradiated, in order to maximize the chance of observing abscopal effects in the thymus. In order to determine that changes in thymic weight were actually due to changes in cell population and did not merely reflect changes in the fluid content of the thymus, measurements were made of the total deoxyribonucleic acid (DNA) content of the thymus as well as of its fresh weight. The thymus was examined at 48 hours after irradiation, the same time interval as in the work of Leblond and Segal. Our results at this time suggest that almost the whole of the effect of abdominal irradiation on the thymus is due to the scattered radiation which affects the thymus directly; it was not possible to confirm the existence of an appreciable indirect or abscopal effect in animals with or without adrenal glands. At times later than 48 hours and after a smaller dose of abdominal irradiation, an abscopal effect on the thymus can be demonstrated, but this

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is due primarily to a decrease in the intake of food and not to any specific, radiation-induced increase in adrenal activity.[7]

METHOD

Male albino rats of the laboratory's inbred stock were used when they were 45–66 days old and from 160–250 gm. in weight. In each experiment there were 4 litter mates which had been housed together since weaning. The animals were irradiated only after having been anesthetized by intraperitoneal amylobarbitone sodium (6–7 mg. per 100 gm.) and all the 4 rats from one litter were anesthetized together. In experiments involving adrenalectomy and part body irradiation, there were in each litter 2 unirradiated controls (1 adrenalectomized and 1 sham-operated) and 2 irradiated rats (1 adrenalectomized and 1 sham-operated but both given the same radiation treatment). The operated rats were given irradiation only to the caudal half or quarter of the body. In other experiments with intact animals, 1 rat was an unirradiated control and the other 3 were given 25 r, 50 r, and 100 r, respectively, either to the cephalic half of the body or to the whole body.

Operations were performed at the time when the animals were under the pre-irradiation anesthesia. The technique of adrenalectomy and of the sham-operations is recorded elsewhere.[7] There were no deaths after adrenalectomy. When each operated animal was killed and its thymus removed, it was inspected to see if adrenal tissue could be seen. No accessory adrenal glands have yet been found in our laboratory stock.

On all occasions the choice of treatment and the order of treatment was determined by drawing cards. Roentgen irradiation was given with 250 kv. peak therapy settings, each with a stepped filter, half value layer of 1.2 mm. Cu. The beam was always directed upwards.[4] Operated rats were given 2,000 r at 78 r per minute, focal skin distance 62 cm., or 5,000 r at 276 or 290 r per minute, focal skin distance 32 or 34 cm. The unoperated rats received their dose either at 5.9 r per minute, focal skin distance 152 cm., or at 276 r per minute; the results are separately recorded. The stated doses are "exposure" doses, *i.e.*, the dose measured in air at the position the center of an animal would occupy.

The anesthetized rats were laid belly down on a piece of brown paper to minimize heat losses by conduction to metal. When whole body irradiation was given, the paper was laid over a layer of cotton wool 1 cm. thick. When part body irradiation was given, the rat was placed partly on the cotton wool and partly on a triple sheet of lead, each sheet being 2 mm. thick. When only the caudal or cephalic half of the body was to be irradiated, the rat was so arranged that the junction between the cotton wool and lead lay immediately under the margin of the rib cage as determined by palpation *in situ*. When the caudal quarter of the body was to be irradiated, the junction lay midway between the margin of the rib cage and the anus.

After the radiation exposures had been made, the 4 rats of the litter were returned to their living cage for 48 hours and then killed. Most of the litters were deprived of all food for this period but drinking water was available *ad libitum*. Salt supplements were not given. The thymus glands were dissected out and weighed; and the total DNA-phosphorus was extracted and determined as described elsewhere.[7] The thymus glands of adult rats have not given as consistent results as the lymph nodes of adult rats or the thymus glands of young growing rats, for reasons which are not understood. Physiologic involution is already beginning in the thymus of male rats of the age and size used in these experiments. In one month all the 5 litters examined gave DNA-P values averaging about half the values obtained earlier and later, even though lymph node determinations (on other animals) made during the same month were within the expected normal range. Two other litters examined at other dates gave similarly low values but only

the series of 5 has been omitted from the results.

After all the biologic work had been done, measurements were made in a phantom of Mix-D wax (a tissue equivalent material) of the scattered dose which might have been expected to reach the thymus as a result of irradiation of the caudal half of the body by the method described above. Baldwin BD2 ionization chambers were used, with cylinders approximately 12 mm. deep and 9 mm. in diameter and a very small air volume about 2 mm. from one end. The measurements were made with the gas volume 8–10 mm. from the ventral surface of the phantom and the chamber in the midline and in the position of the manubrium of the sternum. In the anesthetized rats, the sternal notch was 6 cm. from the edge of the lead shield when the caudal half of the body was irradiated and 9.5 cm. away when the caudal quarter of the body was irradiated. The scattered dose in the phantom was determined when the central axis of the chamber was 5.5 cm. and 9.0 cm., respectively, from the edge of the lead. The dose rate was then 1.3 and 0.5 per cent, respectively, of the dose rate measured by the same chamber in the same position and with the same tube output but with the cranial half of the phantom irradiated instead of the caudal.

RESULTS

In order that the results can be directly compared with those of Leblond and Segal,[9] the absolute values for thymic weight and DNA-P are given in Table II but the ratio of the value in an irradiated rat to that of its unirradiated litter mate is perhaps a more valuable index of effect (Table III). Comparisons within litters exclude a certain amount of between-litter variation and this may be especially useful in study of the thymus when its physiologic involution is beginning. Young mature rats were deliberately chosen for this work because experiments on the thymus of recently weaned rats had already failed to show any specfic adrenal response to ir-

Table I

THYMIC WEIGHT IN INTACT AND ADRENALECTOMIZED RATS GIVEN 1,980–3,680 r IRRADIATION TO THE ABDOMEN

	Results of First Series[11] (males only)		Results of First and Second Series Combined[8] (males and females)		Results of Second Series* (females only)	
	Thymic Weight (mg.)	No. of Rats	Thymic Weight (mg.)	No. of Rats	Thymic Weight (mg.)	No. of Rats
Control Rats						
Intact	190	7	190	12	190	5
Adrenalectomized	183	4	208	6	258	2
Abdominally Irradiated Rats						
Intact	59	7	57	10	52	3
Adrenalectomized	173	6	150	9	104	3
	Mean Value for the Thymic Weight†					
Irradiated Rats						
Intact	31		30		28	
Adrenalectomized	94		72		40	

* Computed by analysis of the combined results of the two series.
† Given as a percentage of the mean value in controls.

Table II

THYMIC WEIGHT AND DNA-P AT 48 HOURS AFTER PART BODY IRRADIATION AND THE CHANGE IN BODY WEIGHT OVER THE 48 HOUR PERIOD

Area Irradiated	Caudal Half	Caudal Half	Caudal Half	Caudal Half	Caudal Quarter
Dose (r)	5,000	5,000	2,000	2,000	5,000
Postirradiation Regimen	Starved	Fed	Fed	Starved	Starved
Age at Death (da.)	52	52	53	57	62
Body Weight of Sham-operated Controls at Death (gm.)	159	213	198	178	199
	Change in Body Weight (gm.)*				
Sham-operated Rats					
Control	−27 (6)	+ 5 (5)	+ 6 (4)	−32 (8)	−36 (3)
Irradiated	−25 (6)	−17 (5)	−10 (4)	−30 (8)	−31 (3)
Adrenalectomized Rats					
Control	−31 (6)	−12 (5)	− 9 (4)	−33 (8)	−34 (3)
Irradiated	−24 (4)	−20 (5)	−14 (4)	−28 (7)	−35 (3)
	Thymic Weight (mg.)*				
Control Rats					
Sham-operated	428 (6)	515 (5)	529 (4)	432 (8)	360 (3)
Adrenalectomized	521 (6)	521 (5)	559 (4)	502 (8)	477 (3)
Irradiated Rats					
Sham-operated	247 (6)	251 (5)	355 (4)	306 (8)	340 (3)
Adrenalectomized	280 (4)	313 (5)	439 (4)	391 (7)	447 (3)
	Total Thymus DNA-P (mg.)†				
Control Rats					
Sham-operated	1.9 (44)	1.7 (32)	1.8 (34)	1.3 (30)	1.0 (27)
Adrenalectomized	2.1 (40)	1.7 (31)	1.6 (31)	1.5 (31)	1.4 (29)
Irradiated Rats					
Sham-operated	1.2 (48)	0.9 (34)	1.4 (37)	1.0 (33)	1.0 (28)
Adrenalectomized	1.4 (51)	1.0 (33)	1.6 (35)	1.1 (28)	1.3 (28)

* The numbers in parentheses give the number of rats on which each mean value is based.
† The numbers in parentheses give the concentration of DNA-P (μg./10 mg. thymus).

radiation[7] and it was conceivable that such a response might be shown by more mature animals of an age and size comparable to those used by Leblond and Segal.[9] For the same reason, male rats were used exclusively since the adrenal effect observed by these workers was found in male animals but not, apparently, in females (Table I).

Abdominal irradiation of rats with 2,000–5,000 r leads to a reduced food intake and to a loss in body weight of 7–10 per cent even at 48 hours, before diarrhea becomes gross. Adrenalectomy alone led to the same degree of loss in body weight as 2,000 r irradiation, but the combined effects of adrenalectomy and abdominal irradiation were less than the sum of the two alone, presumably because a reduced food intake is common to both (Table II). With complete deprivation of food, the loss in body weight was slightly less in irradiated than in unirradiated animals, presumably because of the gastric retention which follows abdominal irradiation.

Table III

THYMIC WEIGHT AND DNA-P AT 48 HOURS AFTER PART BODY IRRADIATION SHOWN AS A PERCENTAGE OF THE VALUE IN THE UNIRRADIATED LITTER MATE (MEAN ± SE)*

Area Irradiated	Caudal Half	Caudal Half	Caudal Half	Caudal Half	Caudal Quarter
Dose (r)	5,000	5,000	2,000	2,000	5,000
Postirradiation Regimen	Starved	Fed	Fed	Starved	Starved
Thymic Weight	(4)	(5)	(4)	(7)	(3)
Sham-operated Rats	57 ± 4	50 ± 5	67 ± 3	71 ± 4	94 ± 5
Adrenalectomized Rats	58 ± 2	61 ± 8	79 ± 7	78 ± 6	94 ± 3
Total Thymic DNA-P	(4)	(4)	(3)	(7)	(3)
Sham-operated Rats	68 ± 2	50 ± 5	80 ± 14	72 ± 3	97 ± 5
Adrenalectomized Rats	72 ± 4	62 ± 15	102 ± 15	69 ± 5	90 ± 6

* The numbers in parentheses give the number of litter mate pairs on which the mean values are based.

In unirradiated animals starvation reduced thymic weight, and in starved animals adrenalectomy increased it (Table II); thus, adrenalectomy in fed animals produced little change because it also led to a reduction in food intake. The DNA-P content of the thymus was less affected by these measures but, in all 17 pairs of starved litter mates, it was greater in the adrenalectomized than in the sham-operated animal. The effect of starvation alone cannot be determined from the data because of the variation in DNA-P between litters.

The reduction in thymic weight and in DNA-P in starved animals given 5,000 r to the caudal half of the body was proportionately the same in adrenalectomized and in sham-operated animals (Table III) suggesting that the effect of abdominal irradiation on the thymus was not mediated via the adrenal glands. In fed animals there was a statistically nonsignificant difference in the direction expected if adrenal activity was relevant.

In the experimental arrangement which was used, the adrenal glands were near the boundary between the directly irradiated and the shielded areas of the body and it was conceivable that the radiation dose which the adrenal glands received would be enough to damage them and so prevent an adrenal reaction which otherwise would have occurred. To check this point the dose to the adrenal glands was reduced (a) by reducing the dose to the caudal half of the body to 2,000 r and (b) by giving 5,000 r to the caudal quarter of the body, thus ensuring that only distant scattered radiation could reach the adrenal glands. In neither case (Table III) was there a significant difference between sham-operated and adrenalectomized starved animals in the degree of reduction in thymic weight or DNA-P, though the effect of 5,000 r to the caudal quarter of the body was so small as to be in itself statistically nonsignificant.

Experiments with 2,000 r abdominal irradiation were also done with food available *ad libitum* and, as after 5,000 r, the effect of adrenalectomy was statistically nonsignificant. Nevertheless, it was noticeable after both the 5,000 r and 2,000 r doses that, in both thymic weight and thymic DNA-P, the differences between sham-operated and adrenalectomized rats were greater in fed than in starved animals (Table III) and that the differences in the fed animals were always in the direction expected if adrenal activity played some part in mediating the effects of abdominal irradiation. However, in view of the well-known effect of irradiation on food intake and of food intake on the thymus gland (Table II), it must be concluded that data on starved animals provide more reliable

TABLE IV

THE DIRECT EFFECT OF IRRADIATION ON THE THYMIC WEIGHT AND DNA-P OF MALE RATS 48 HOURS AFTER EXPOSURE UNDER DIFFERENT EXPERIMENTAL CONDITIONS*

Dose Rate (r/min.)	Area Irradiated	Postirradiation Regimen	Age (da.)	Thymic Weight			Thymic DNA-P		
				25 r dose	50 r dose	100 r dose	25 r dose	50 r dose	100 r dose
276	Cranial half	Starved	45	89	73	40	75	71	48
			51	75	78	55	74	72	39
5.9	Cranial half	Starved	51	77	56	40	70	51	28
			57	80	72	37	84	45	38
			60	97	60	45	—	—	—
5.9	Whole body	Starved	54	75	68	52	70	66	36
			57	90	66	38	96	69	36
5.9	Cranial half	Food *ad libitum*	51	95	71	46	78	50	26
			52	86	78	45	96	92	42
			56	81	64	45	—	—	—

* Each value is for an individual rat expressed as the prcentage of that in its litter mate control.

evidence on adrenal activity after irradiation than data derived from litters with access to food.

After direct irradiation of the thymus, the concentration of DNA-P was slightly decreased, as would be expected, but, after irradiation of the caudal half of the body with a dose sufficiently large to affect the thymus, the DNA-P concentration was increased in 7 of the 8 groups (Table II). This interesting qualitative difference may be evidence for the existence of tissue dehydration following abdominal irradiation at a time before there is overt diarrhea.

The Assessment of Scatter. One obvious factor to consider when examining the effect of abdominal irradiation on the thymus is the direct radiation damage due to scattered radiation. Before any physical measurements of scatter were made, animals were given small doses of radiation directly to the chest in order to provide a biologic calibration curve from which could be derived the direct dose required to produce the amount of damage actually measured after the different doses of abdominal irradiation. It was realized that the actual dose rate at the thymus due to scatter from abdominal irradiation would be a certain percentage of the direct dose rate, so two sets of experiments were made, at 276 r per minute and at 5.9 r per minute, a dose rate of about 2 per cent of the 276–290 r per minute used for the 5,000 r abdominal dose. The data are given in Table IV and it can be seen that, if there were differences in effect between the two dose rates, between fed or starved animals, or between whole body or part body irradiation, the differences were quantitatively small. The pooled results may, therefore, be used legitimately as a calibration curve for the data in Table III on starved and sham-operated animals.

It can be seen that the effect on the thymus of 2,000 r or 5,000 r to the caudal half of the body could be accounted for by scatter if the dose at the thymus due to scatter was between 1.0 and 2.5 per cent of the abdominal dose. At both doses the estimate from change in DNA-P was close to the estimate from change in thymic weight, averaging 1.2 per cent for the dose of 5,000 r and 2.1 per cent for the dose of 2,000 r. After this deduction was made, direct measurement in a 200 gm. rat phantom, irradiated in the standard experimental manner, showed that the physically

scattered dose at the thymus was, in fact, of the order of just over 1 per cent. Similarly, the dose at the thymus from 5,000 r to the caudal quarter of the body must have been rather less than 0.5 per cent, judging from the biologic calibration curve, and was measured physically as 0.5 per cent. For a variety of reasons, the physical measurements of scatter are inevitably only an approximate measurement of the dose due to scatter which is actually received by the thymus gland *in vivo*[6] and the agreement between the biologic and physical dosimetry is probably really quite good.

DISCUSSION

The results reported here differ in two ways from those reported by Leblond and Segal:[9] (a) the degree of reduction in thymic weight following a given dose of abdominal irradiation to sham-operated animals was considerably less than in their work, even though a larger fraction of the body was irradiated; and (b) the effect of adrenalectomy was very much less than in the combined results reported by them, although it was quite similar to their second series as shown in Table I of this paper.

There are several differences in the experimental details which may have a bearing on the differences in the results. Their adrenalectomized and sham-operated irradiated rats were matched pairs, although their unirradiated controls were not matched with the irradiated animals, whereas our animals were always litter mates. Their animals were irradiated unanesthetized and tied down to a board; our animals were always unconscious. Their animals were adrenalectomized 2–5 days before irradiation and were quite sick at autopsy 48 hours later; in fact, it is stated that some died shortly before this time. (It is also stated that some animals were killed at 66 hours, although the results on all the animals appear to have been combined together.) Our animals were adrenalectomized immediately before irradiation; none died or were moribund at 48 hours, the time when all were killed. In both cases the ventral surface of the rats faced the roentgen-ray tube and the duration of the radiation exposures was similar. The rat stocks must have differed, since the thymic weight of Leblond and Segal's controls was about half that of our controls.

It might be thought that anesthesia would produce sufficient anoxia to modify radiation responses *in vivo*. However, barbiturate anesthesia, as used here, did not appear to modify the response of the thymus in young rapidly growing rats to direct irradiation.[7] On the other hand, tying a conscious animal to a board might possibly be a strong stress stimulus which would affect the thymus in sham-operated animals with intact adrenal glands but not in adrenalectomized animals. If so, the results of Leblond and Segal[9] could perhaps have been explained away as illustrating the phenomenon of stress, with irradiation as a minor factor in the total situation. However, such an explanation cannot account for the results in Leblond and Segal's second series, as illustrated in Table I, where the effect of the irradiation procedure in adrenalectomized animals was so substantial. The remaining factor, the variation in the length of time elapsing between adrenalectomy and examination, is of unknown significance, and it must be concluded that no wholly valid explanation is available at present of our failure to confirm the findings of Leblond and Segal. Our results did show that control of food intake is a necessary part of experiments designed to investigate adrenal activity after irradiation, and in other work reported elsewhere[7] a change in food intake after 500 r abdominal irradiation was found to be a complete explanation of the changes in the thymus occurring 3–5 days after exposure.

The results recorded in Table III seem to show that the effect of abdominal irradiation on the thymus depended scarcely at all on adrenal activity. On the other hand, the degree of effect was just that expected from the scattered radiation which must inevitably be absorbed within the cells of the thymus gland whenever the abdomen

is irradiated. Using a localized abdominal dose of 3,564 rep of deuterons (RBE = 1), Bond *et al.*[3] failed to detect any appreciable change in thymic weight until more than three days after irradiation and they concluded that "with a high energy deuteron beam lateral scatter from its path in tissue is negligible.

It is, on the whole, a little surprising to find so little evidence of adrenal activity at 48 hours after large doses of abdominal irradiation. In rats intestinal damage following lethal exposures leads to marked changes in the water and salt content of the body, which are grossly obvious by 72 hours. The equivocal evidence obtained in the present experiments that adrenal activity might be a minor factor at 48 hours is perhaps consistent with increased adrenal activity at 72 hours.

The changes in the weights of organs provide a simple means of following the evolution of radiation damage but changes in organ weight may not always reflect proportionate changes in cell populations. In the thymus of the adult rat, DNA synthesis is normally small and, unless the rate of DNA synthesis within an organ can vary quite considerably, there is little error in taking DNA measurements as a more accurate reflection of cell population than change in organ weight. As against this, measurements of DNA may be less precise than simple measurements of weight (Table IV) but, on the whole, they are not much less accurate, judging by the results reported here. With direct irradiation there is a decrease in DNA concentration; consequently, the DNA content of the thymus is a slightly more sensitive index of radiation effect than the weight of the organ.

SUMMARY

1. The degree of damage to the thymus caused by direct irradiation with 25–100 r was not altered by a fifty fold change in dose rate.

2. It was not possible to confirm the often-cited finding that the effect of abdominal irradiation on the thymus is due to stimulation of the adrenal gland. Abdominal irradiation of starved adult rats with 2,000 or 5,000 r caused a 25–40 per cent reduction in thymic DNA-P and in thymic weight 48 hours later. However, adrenalectomy scarcely modified the degree of change which could be almost wholly accounted for by the scattered radiation which is presumed to reach the thymus. Physical and biologic measurements of the scattered dose were in agreement.

3. In control animals, adrenalectomy led to an increase in the weight of the thymus, starvation to a decrease. In view of the effect of abdominal irradiation on food intake and the effect of food intake on the thymus, evidence from starved animals is considered to be more reliable than evidence from animals with free access to food when investigating the possible existence of abscopal effects of abdominal irradiation on the thymus.

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EFFECTS OF COMBINED ROENTGEN IRRADIATION AND CHEMOTHERAPY ON TRANSPLANTED TUMORS IN MICE*

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COMBINATIONS of irradiation and chemotherapeutic agents have been employed in treating tumors in animals as well as in man in the hope of improving the therapeutic effect. The voluminous literature on this subject has been reviewed by Bane *et al.*[2]

Heidelberger *et al.*[5] studied the effect of a single dose of 1,500 r to 2,000 r of roentgen rays alone and in combination with 5-fluorouracil (5-FU) 20 mg./kg. for 7 days on the 755 mammary adenocarcinoma and the sarcoma 180 in mice. They reported complete disappearance of all tumors after 28 to 31 days of observation. Both tumors continued to grow with 5-FU treatment alone, while the roentgen-ray treatments arrested the growth of the sarcoma and inhibited the mammary adenocarcinoma but did not cause complete regression.

Hall *et al.*[4] observed promising initial responses in squamous cell carcinomas of the lung and the head and neck as well as in certain isolated tumors of other origin, but no long term effects were mentioned.

The purpose of this paper is to report on the enhanced effect of multiple exposures of local roentgen irradiation given in conjunction with the antimetabolite 5-fluorouracil,* the antibiotic actinomycin P_2* (P_2) and the alkylating agent Cytoxan* on transplanted sarcoma 180 in Swiss Webster albino and mammary adenocarcinoma in Z inbred mice.

* 5-fluorouracil was supplied by Hoffmann-LaRoche, Inc.; actinomycin P_2 by Chas. Pfizer and Co., Inc.; and Cytoxan by Mead Johnson & Company.

MATERIAL AND METHODS

TRANSPLANTATION OF TUMORS

Female Swiss Webster albino mice weighing 25 to 30 gm. (9 to 11 weeks of age) from Taconic Farms, Germantown, New York, were used for maintaining the sarcoma 180 originally obtained from the Wisconsin Alumni Research Foundation through the McArdle Memorial Laboratory.

Male Z (Bittner C3H) mice weighing 20 to 25 gm. (6 to 10 weeks of age) bred by sister to brother matings in our laboratories were used for transplanting the mammary adenocarcinoma which originated spontaneously in one of the older female mice. While the sarcoma 180 had been transferred over innumerable generations in different hosts, the adenocarcinoma in Z mice had been transferred only twice by serial transplantation in young Z male mice.

The transplantation was performed by injecting a 10 per cent suspension of fresh wet tumor tissue pulp from the tissue press in sterile physiologic saline. A volume of 0.05 ml. was injected subcutaneously into the ventral aspect of the right hind leg. The tumor growth was relatively uniform with close to 100 per cent takes with both tumors. The sarcoma 180 produced palpable tumor nodules 4 to 5 days after transplantation and the average survival in the untreated groups varied between 15.4 and 27.3 days.

The adenocarcinoma had a slower growth rate and produced palpable tumor nodules

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after a latent period of about 2 to 3 weeks. The tumors in nontreated control mice always grew progressively until they became huge, ulcerated, and infected; the animals died usually within 10 weeks. The mice were kept at a room temperature of 75 to 80° F. under standard laboratory conditions in suspended wire-bottom cages, and fed Purina fox chow and tap water *ad libitum*. They were examined at weekly intervals, weighed and the tumors measured with calipers.

IRRADIATION

The x-ray treatments were started 4 or 5 days after transplantation of the sarcoma 180, and after 2 to 3 weeks in the case of the adenocarcinoma, and only after a definite tumor nodule could be palpated and measured. The treatments were given with a superficial x-ray machine operated at 140 kv. peak with 1 mm. aluminum filter at 15 cm. focal skin distance, and a dose rate of 232 ± 10 per cent r/min., as determined with Victoreen thimble ionization chambers inserted at the position of the tumors. The half value layer was 4 mm. of aluminum. The treatments were given locally to the right leg with the tumor transplant secured in the radiation field by small battery clamps attached to the feet, while the rest of the body was outside a lead cylinder mounted on the x-ray machine tube housing.[6] This set-up ensured constant geometric relationships between the tumors and the radiation beam. In spite of a rather pronounced anode effect at this short distance, a uniform dose was given by randomization of the animals in the radiation device. No anesthetic was administered and the mice were under little stress while being irradiated. Ten mice were irradiated simultaneously.

The radiation treatments were kept uniform in all experiments, using a daily dose of 300 r for 5 consecutive days per week until a total of 17 treatments had been given or a total accumulated dose of 5,100 r over a period of 23 days. In one experiment a lower dose was used, 250 r on alternate days for a total dose of 3,000 r. The rationale for employing the above dosage schedules was to approximate those frequently used in patients.

CHEMOTHERAPY

Preliminary toxicity studies were carried out on tumor bearing and normal mice with each of the compounds to determine the maximal dose that could be tolerated. The 5-fluorouracil was injected intraperitoneally while actinomycin P_2 and Cytoxan were given intravenously in volumes of about 0.2 ml. The 5-fluorouracil was dissolved in sterile physiologic saline, the actinomycin P_2 in a 5 per cent (V/V) aqueous acetone solution and the Cytoxan in sterile double distilled water. The largest dose which did not result in any death among a large number of mice was chosen for the combined therapy and was as follows:

5-fluorouracil:

(1) *Swiss albino mice:*
35 mg./kg. animal body weight daily for 5 days or the same dose for 4 days followed by 17.5 mg./kg. on the fifth day and then twice weekly for 2 weeks (Table I).

(2) *Z mice:*
30 or 35 mg./kg. animal body wieght daily for 5 days (Table II).

Actinomycin P_2:

Swiss albino mice:
1.4 mg./kg. animal body weight for 5 days or the same dose for 4 days followed by 0.7 mg./kg. on the fifth day and then twice weekly for 2 weeks, or 1.0 mg./kg. for 3 days followed by 0.5 mg./kg. on the fourth day and then twice weekly for 2 weeks (Table I).

Cytoxan:

Swiss albino mice:

25 to 36 mg./kg. animal body weight for 3 days followed by 12.5 to 18 mg./kg. on the fourth day and then twice weekly for 2 weeks (Table I).

The injections of the chemicals were started in the case of the sarcoma 180, 8 days and with the mammary adenocarcinoma, 2 to 3

Table I

SURVIVAL OF MICE BEARING SARCOMA 180

Treatment	No. of Mice	Chemical Dose (mg./kg.)	X-ray Dose (r in 3 days)	Average Survival (days ± S.E.)	No. with Complete Regression
Controls	9	0	0	25.6±4.5	0
5-FU and x-rays	9	35 ×4 17.5×6	5×100	73.9±4.1[1]	6
Actinomycin P_2 and x-rays	9	1 ×3 0.5×6	5×100	62.1±3.9[1]	4
Controls	10	0	0	18.8±3.3	0
5-FU alone	10	35 ×5	0	24.5±3.4[2]	0
5-FU and x-rays	10	35 ×4 17.5×5	5×100	62.8±7.2[3]	2
Actinomycin P_2 and x-rays	10	1.4×4 0.7×5	5×100	49.2±9.0[3]	2
Controls	9	0	0	15.4± 1.1	0
Actinomycin P_2 alone	9	1.4×5	0	14.9± 1.1	0
X-rays alone	9	0	5×100	38.6± 5.3[4]	0
Actinomycin P_2 and x-rays	10	1.4×5	5×100	63.4±12.3[4]	4
Controls	10	0	0	27.3±3.9	0
X-rays alone	10	0	5×100	56.9±5.3[5]	3
Cytoxan alone	10	33 ×3 16.5×7	0	29.9±6.1	0
Cytoxan alone	10	36 ×3 18 ×7	0	31.5±5.9	1
Cytoxan and x-rays	10	33 ×3 16.5×7	5×100	61.6±7.4[5]	4
Cytoxan and x-rays	10	36 ×3 18 ×7	5×100	50.8±5.0	1
Control	9	0	0	21.0±4.1	0
X-rays alone	9	0	5×100	39.8±4.7[6]	1
Cytoxan alone	9	25 ×3 12.5×7	0	22.7±4.7	0
Cytoxan alone	9	30 ×3 15 ×7	0	21.2±4.2	0
Cytoxan and x-rays	9	25 ×3 12.5×7	5×100	34.8±6.1	0
Cytoxan and x-rays	9	30 ×3 15 ×7	5×100	49.8±2.7[6]	1
5-FU and x-rays	9	35 ×4 17.5×6	5×100	40.6±6.0	3

[1] Significance of difference: 5-FU and x-rays versus actinomycin P_2 and x-rays $P=0.05$.
[2] Significance of difference: controls versus 5-FU alone $P=0.25$.
[3] Significance of difference: 5-FU and x-rays versus actinomycin P_2 and x-rays $P=0.25$.
[4] Significance of difference: x-rays alone versus actinomycin P_2 and x-rays P=[illegible].
[5] No significant difference between x-rays alone and Cytoxan and x-rays.
[6] Significance of difference: x-rays alone versus Cytoxan and x-rays $P=0.09$.

TABLE II

SURVIVAL OF MICE BEARING MAMMARY ADENOCARCINOMA

Treatment	No. of Mice	Chemical Dose (mg./kg.)	X-ray Dose (r)	Average Survival (days ± S.E.)	No. with Complete Regression
Controls	4	0	0	42.3 ± 5.8	0
5-FU alone	5	35×5	0	41.6 ± 12.4	0
X-rays alone	5	0	3,000 in 28 days	62.0 ± 5.6	0
X-rays and 5-FU	4	35×5	3,000 in 28 days	62.0 ± 9.0	0
Controls	7	0	0	49.4 ± 4.3	0
5-FU alone	7	30×5	0	48.9 ± 5.5	0
X-rays alone	7	0	5,100 in 23 days	74.1 ± 2.7[1]	0
5-FU and x-rays	7	30×5	5,100 in 23 days	79.1 ± 9.1[1]	0
Controls	12	0	0	31.0 ± 1.3	0
5-FU alone	12	30×5	0	42.0 ± 2.5	0
X-rays alone	12	0	5,100 in 23 days	53.3 ± 3.4[2]	0
5-FU and x-rays	12	30×5	5,100 in 23 days	72.8 ± 2.6[2]	1
Controls	10	0	0	43.5 ± 1.2	0
X-rays alone	10	0	5,100 in 23 days	53.8 ± 2.6[2]	0
5-FU and x-rays	10	30×5	5,100 in 23 days	71.2 ± 1.8[2]	0

[1] No significant difference between x-rays alone versus 5-FU and x-rays.
[2] Significance of difference: x-rays alone versus 5-FU and x-rays P = 0.001.

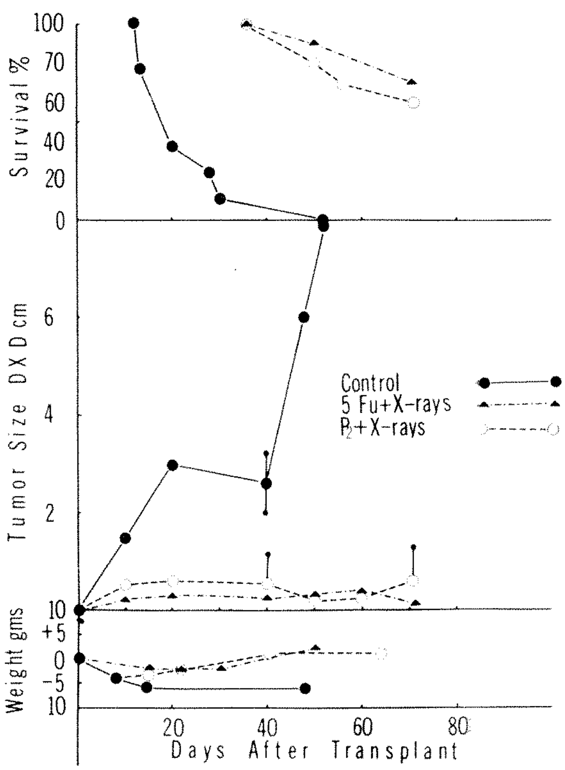

FIG. 1. A comparison of effects of 5-FU and x-rays with P_2 and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

weeks after the transplantation when the tumors were distinctly palpable and measurable.

RESULTS

Each group of animals was analyzed with respect to the survival times of the tumor bearing animals expressed in terms of the average survival (Table I and II) and in terms of fraction surviving at different time intervals (Fig. 1–9). The growth rates of the tumor transplants were computed as average tumor size expressed by the products of two opposing diameters and the average body weights at different time intervals also recorded (Fig. 1–9). The number of animals exhibiting complete tumor regression are listed in Table I and II.

The results fall in two separate groups: (a) those obtained with sarcoma 180 in albino Swiss Webster mice, and (b) those obtained with mammary adenocarcinoma in inbred mice of the Z strain.

Sarcoma 180. In the analysis of the survival times, it was apparent that the animals which received combined 5-fluorouracil and x-ray therapy outlived all the others. The average survival times in two different experiments were 73.9 and 62.8 days, respectively, as compared with 25.6 and 18.8 days in the nonirradiated controls and 62.1 and 49.2 days in animals receiving combined actinomycin P_2 and x-ray treatments. The difference between combined treatments with 5-fluorouracil and x-rays and actinomycin P_2 and x-rays was significant in the first experiment ($P = 0.05$).

In the analysis of the growth rates of the

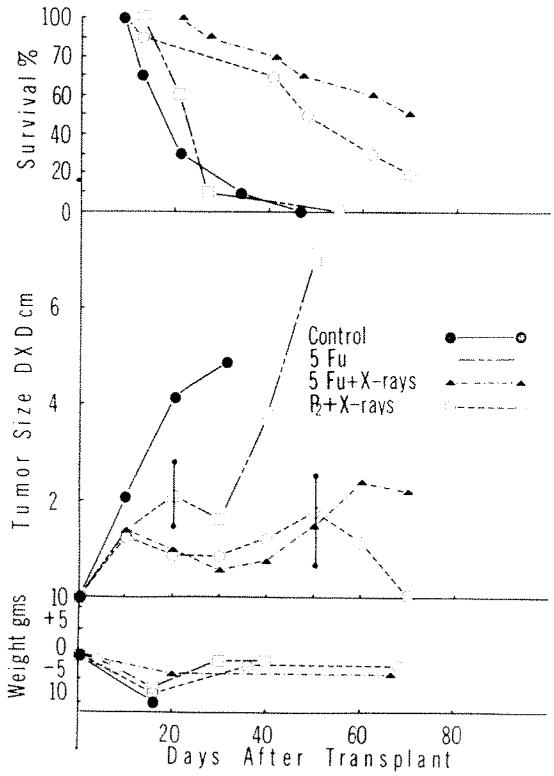

FIG. 2. A comparison of effects of 5-FU, 5-FU and x-rays, and P_2 and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

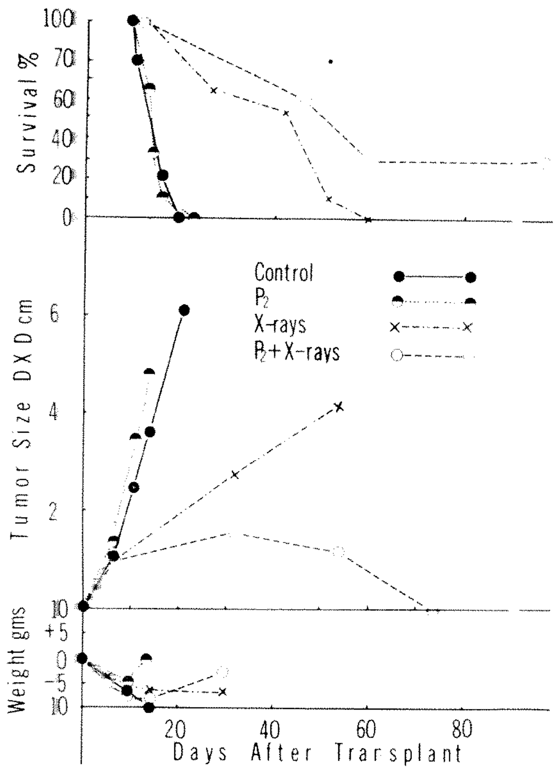

FIG. 3. A comparison of effects of P_2, x-rays, and P_2 and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

tumors, a marked inhibition was evident in the group which received combined treatments when compared with the less pronounced effect from chemotherapy or x-ray therapy alone. This was demonstrated when irradiation in combination with both 5-fluorouracil and actinomycin P_2 was used as shown in Figure 1, 2 and 3.

In 8 out of 19 animals treated with 5-fluorouracil and x-rays and in 10 out of 29 treated with actinomycin P_2 and x-rays, complete tumor regression occurred. Irradiation alone failed to produce complete tumor regression although tumor growth was retarded; nevertheless, all animals died with growing tumors (Fig. 3). The average survival time in this group was 38.6 days, as compared with 15.4 days in the control and 63.4 days in the group receiving combined treatment with actinomycin P_2 and x-rays. The difference between the average

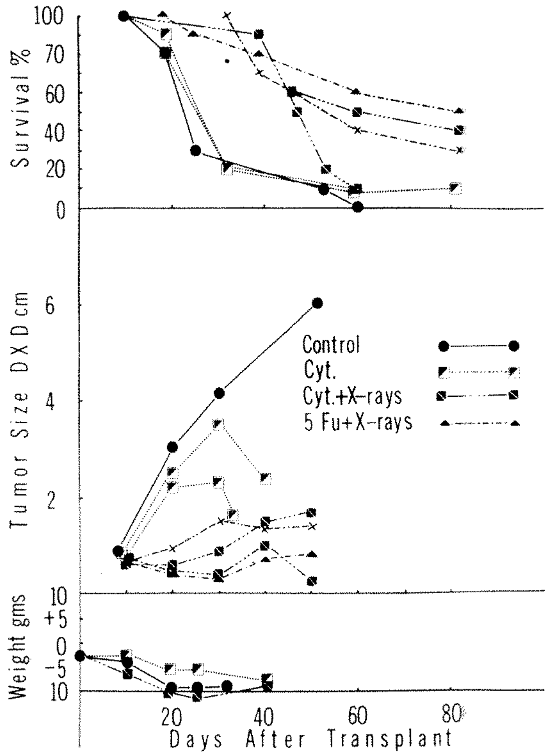

FIG. 4. A comparison of effects of Cytoxan, Cytoxan and x-rays, and 5-FU and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

survival of animals treated with x-rays alone and those receiving combined actinomycin P_2 and x-ray treatment is on the borderline of statistical significance ($P = 0.08$). In this experiment the combined therapy resulted in complete tumor regression in 4 out ot 10 animals while no regression resulted from x-ray treatments alone. Similarly, 5-fluorouracil or actinomycin P_2 alone failed to arrest the growth of these tumors (Fig. 2 and 3).

Owing to the fact that many of the animals which received combined treatments were still alive at the time of writing, the average survival rate expressed in the tables is minimal and will obviously increase as long as these animals survive. Thus, the differences observed will become more significant, since all animals which received chemotherapy or x-ray treatments alone are dead.

In the analysis of the weight curves, it became apparent that the combined therapy resulted in no more weight loss than did the chemotherapy alone. All animals which showed complete tumor regression rapidly regained their weight. Slightly greater weight loss occurred with actinomycin P_2 and x-rays than with 5-fluorouracil and x-rays (Fig. 1, 2 and 3).

The two experiments with Cytoxan are still incomplete. The data obtained suggest that Cytoxan alone in the dose levels employed could not arrest the growth of the tumor nor increase the survival of the animals (Fig. 4 and 5). Cytoxan administered in conjunction with x-rays in dose levels of

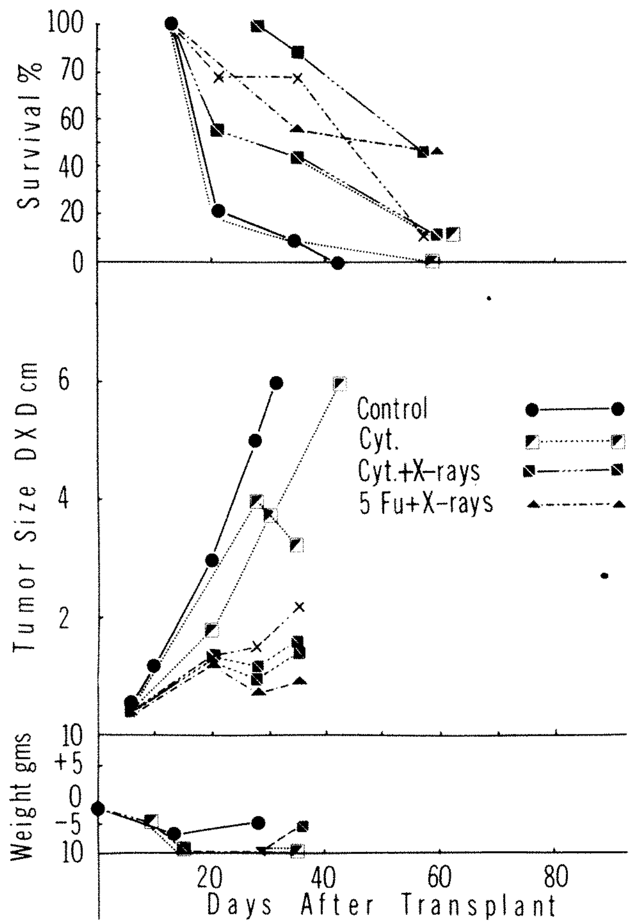

FIG. 5. A comparison of effect of Cytoxan, Cytoxan and x-rays, and 5-FU and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

36 mg./kg. animal body weight appeared too toxic and 25 mg./kg. had no increased effect on the tumor as compared with x-rays alone. Cytoxan administered in combination with x-rays in dose levels of 30 or 33 mg./kg. proved quite effective, however, and caused complete tumor regression in 4 out of 10 animals in one experiment and in 1 out of 9 in the other. Our data suggested the importance of choosing the optimal dose of the chemical for achieving enhanced radiation effects on the tumors (Table I).

The average survival so far compares favorably with that obtained with combined 5-fluorouracil and x-ray treatments in these experiments. Irradiation alone produced complete tumor regression in 3 out of 10 animals of the first and in 1 out of 9 animals of the second experiment, emphasizing that further studies are needed before definite conclusions can be drawn regarding enhancement of radiation effects on the tumors by Cytoxan.

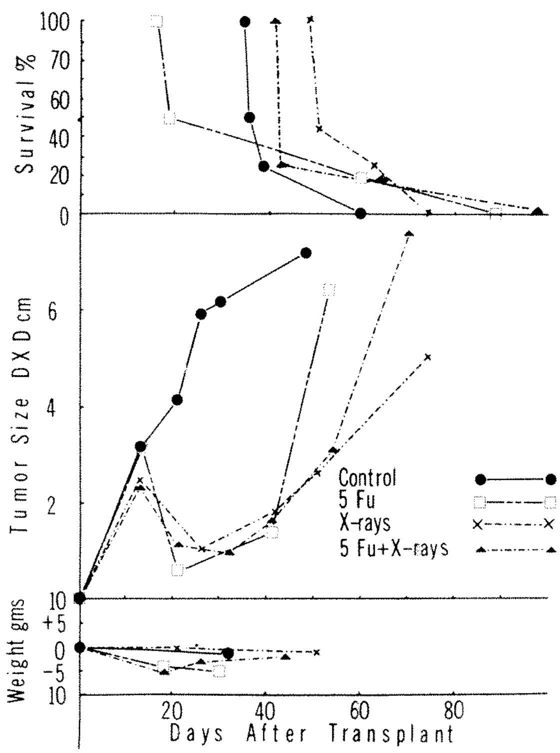

Fig. 6. A comparison of effects of 5-FU, x-rays, and 5-FU and x-rays on tumor size of mammary adenocarcinoma and on survival time and weight curves of their hosts.

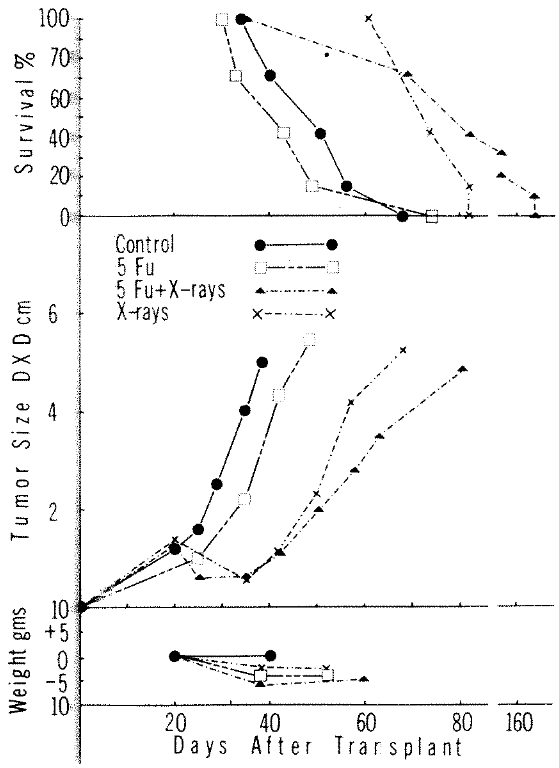

Fig. 7. A comparison of effects of 5-FU, 5-FU and x-rays, and x-rays on tumor size of mammary adenocarcinoma and on survival time and weight curves of their hosts.

Mammary Adenocarcinoma in Z Mice. Experiment No. 1 (Table II) represented a preliminary study with small groups of animals. The doses of 5-fluorouracil and x-rays proved unsatisfactory. These were subsequently changed as the dose of 5-FU proved too toxic and the x-ray dose inadequate. In the second experiment with 7 animals per group, the combination of x-rays and 5-FU treatments resulted in some increase in the average survival time as compared to x-ray treatments alone, but the difference was not statistically significant. All mice died with growing tumors. The weight loss was slight (Fig. 6 and 7).

In subsequent experiments larger numbers of tumor bearing animals were used. Those that received combined x-ray and 5-FU treatments showed a statistically

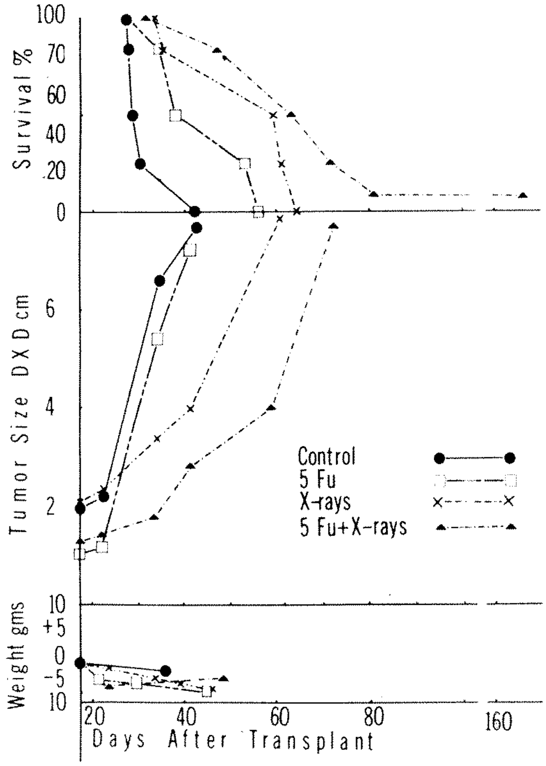

FIG. 8. A comparison of effects of 5-FU, x-rays, and 5-FU and x-rays on tumor size of mammary adenocarcinoma and on survival time and weight curves of their hosts.

significant increase in the average survival time when compared with mice treated with x-rays alone (72.8 and 71.2 days as compared with 42 and 53.8 days, with P=.001 in both experiments). All animals died, however, from progressive tumor growth with 1 exception. In this single mouse the tumor regressed completely and the animal is still alive, 150 days after the transplantation. The slight loss in animal body weight suggested a minimum of toxicity (Fig. 8 and 9). In three experiments the growth of the tumors was more inhibited by the combined treatments than by either chemotherapy or roentgen therapy alone.

DISCUSSION

These experiments were initiated after attempts at evaluating the possible merits of combined chemotherapy and roentgen therapy in far advanced malignancy in humans had given inconclusive results in our institution. Suitable controls in the human studies reported were noticeably absent so that an enhanced antitumor effect by the combination could not be proved unequivocally.

The ready availability of animal controls and the employment of the same tumor in all animals in terms of quantity and time of inoculation obviate the shortcomings of the human studies.

The limitations of studies of this nature in terms of applying the results to clinical work are well recognized. Such limitations are, however, inherent in any type of screening of chemical agents against animal tumors. A good example is the failure of 5-fluorouracil administered alone to produce regression of established transplanted mouse tumors even when given in near

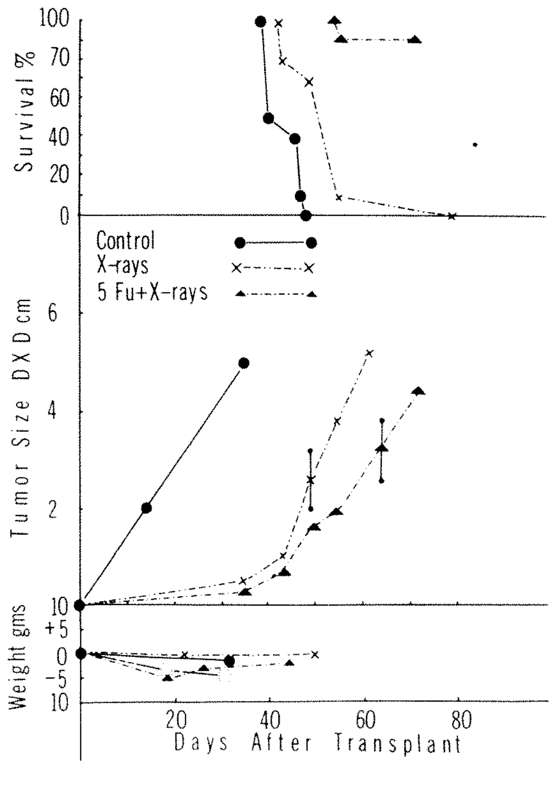

FIG. 9. A comparison of effects of x-rays, and 5-FU and x-rays on tumor size of mammary adenocarcinoma and on survival time and weight curves of their hosts.

lethal doses when it has been demonstrated repeatedly that this compound may result in dramatic regression of advanced tumors of the breast, colon and ovary in the human.[3]

Spontaneous tumors in inbred mice may be preferable for this type of work but they are not readily available in the large numbers necessary for statistical studies. Furthermore, there is no assurance that results obtained with spontaneous tumors have more validity in human tumors than those obtained with transplanted tumors. The great variety of tumors in the human precludes any generalization as to the merits of combined chemo- and roentgen therapy based on results obtained in animal experimentation.

Certain chemotherapeutic agents have shown a preferential antitumor activity against certain types of malignant neoplasms. As all three agents studied in combination with x-ray therapy showed an increased effect over x-ray therapy alone, the compound most likely to produce a response in a given tumor could be chosen for the combined treatment.

Reports from our institution had previously pointed out that irradiation to large flat bones as in the pelvis resulted in marked leukopenia when fluoropyrimidines were subsequently administered.[1] This phenomenon was also observed when Cytoxan was given subsequent to pelvic irradiation. Actinomycin P_2, however, did not produce leukopenia in our animal and human studies and lent itself admirably to combination treatment with irradiation.

CONCLUSIONS

Sarcoma 180 transplanted to Swiss Webster albino mice and mammary adenocarcinoma, originating spontaneously in inbred Z (C3H) mice and transplanted for two generations in the same strain, were used for studies on the effects of combined chemo- and roentgen therapy.

Treatments with 5-fluorouracil, actinomycin P_2 or Cytoxan and fractionated x-ray therapy resulted in increased inhibition of the growth of the tumors as well as prolonged survival of the animals when compared with either chemotherapy or x-ray therapy alone.

Further studies in an attempt to determine the optimal time dose relationship in a wider spectrum of tumors are being pursued currently at our institution.

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In Vivo DOSIMETRY WITH MINIATURE GLASS RODS*

PART I. PHYSICAL ASPECTS AND RECENT DEVELOPMENTS

By STANLEY J. MALSKY, CHARLES G. AMATO, CYPRIAN B. REID, CHARLES SPRECKELS *and* L. MADDALONE

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The glass dosimeter† employed weighs approximately 830 μg., is 1 mm. in diameter and 6 mm. in over-all length. Its use is based upon the principle of radiophotoluminescence,‡ a phenomenon first described by Prizbran[18] thirty-four years ago.

PRINCIPLE AND DESIGN

The dosimeter is comprised of a glass host consisting of barium-potassium-aluminum metaphosphate containing a deliberately added impurity, silver metaphosphate, which acts as the source of the fluorescent activator. The transmission or absorption of ionizing radiation produces many effects, only three of which are of interest in this presentation. They are: the production of photoelectrons, the dissociation of the silver metaphosphate, and the reduction of ionic silver to metallic silver. The last effect is irreversible. When ionic silver is exposed to ultraviolet light, it absorbs, transmits or reflects the ultraviolet rays. However, the metallic silver will alter the frequency and hence the wave length of the incident ultraviolet excitation. The result is the emission of an orange-yellow fluorescence, the intensity of which is directly proportional to the number of metallic silver fluorescent centers present, and hence is directly related to the cumulative radiation exposure. By the proper use of optical by-pass filters and a photomultiplier tube, the fluorescence can be converted into a direct current signal. Due to the linear relationships present, a relative dosimetry system results.

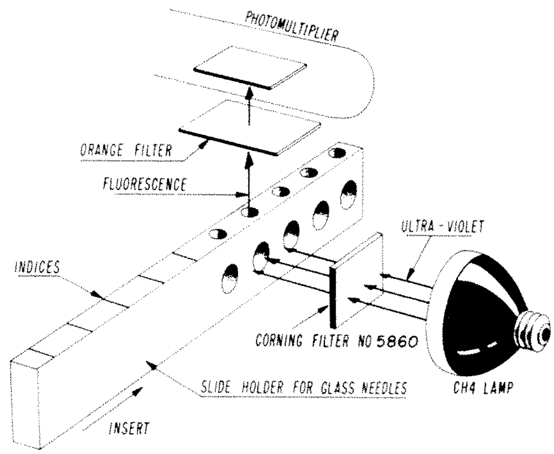

Fig. 1. The glass dosimeters are mounted perpendicular to the ultraviolet source. Fluorescence output is proportional to the amount of radiation received.

Figure 1 illustrates the method by which the fluorescence is produced and converted to an electrical signal. The needles are read in this fluorimeter, called a reader. The reader system employed in this investigation is one developed by Dr. Schulman and his associates[19,20] of the U. S. Naval Research Laboratory.

Figure 2 is a block diagram of the entire reader. The use of an isolating transformer, the autotransformer and the two monitoring voltmeters was an experimental precaution and need not be employed during routine work.

Figure 3 is a schematic diagram of a balanced bridge electrometer amplifier designed by Caldwell[4] and modified by our staff. The range selection is obtained by placing a voltage divider in the input circuit. Batteries supply filament, grid and

† Both regular composition and low Z glass are obtainable from the Bausch and Lomb Optical Co.

‡ Radiophotoluminescence is a phenomenon whereby a material, originally nonluminescent under visible or ultraviolet light, is made responsive to such light excitation by exposure to roentgen or gamma radiation.

* From the Radiophysics Research Section, Radiotherapy Service, Veterans Administration Hospital, Bronx, New York.
Presented at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960.

plate voltage. The value of the screen grid resistor (shown as 27,000 ohms) must be experimentally determined. The proper value permits the current in the arms of the bridge to be balanced when no input signal is applied and the zero potentiometer is in its midposition. This resistance value must be redetermined whenever any circuit parameter is altered.

The reader just described can be assembled for about $600.00. A commercially available reader is under development.* If this reader is used, its linearity and range must be critically evaluated. Any reader should exhibit a linear response and should read up to 10,000 r. A radiation detector should be energy and rate independent and should have either a linear or log response.

Numerous articles have been published in the literature relating to the physical characteristics.[5–10] We are continuing investigations into those properties displayed by the regular glass dosimeter and that of the low Z glass (containing lithium-manganese-aluminum metaphosphate).[12,13] Both types of microdosimeter glass can read up to 10,000 r (with shields), and beyond this limit by measuring the change in optical transmission. The unshielded or bare glass must be considered energy dependent whenever photon energies of less than 1 mev. are encountered.[14] To overcome this, proper shielding must be provided.[15] This was one of the goals of our work, when a minimum diameter shield was evolved so that the entire assembly would permit human *in vivo* measurements. Toxic materials were eliminated from consideration as a shield material. Minimum wall thickness requirements suggested the use of pure gold or platinum; gold was selected due to cost considerations and ease of fabrication.

Figure 4 illustrates a prototype of our final shield design. A properly designed shield must admit a percentage of the softer component of the beam. If the shield is not properly designed, the dosimeter may fail

* Literature is available from the Bausch and Lomb Optical Co.

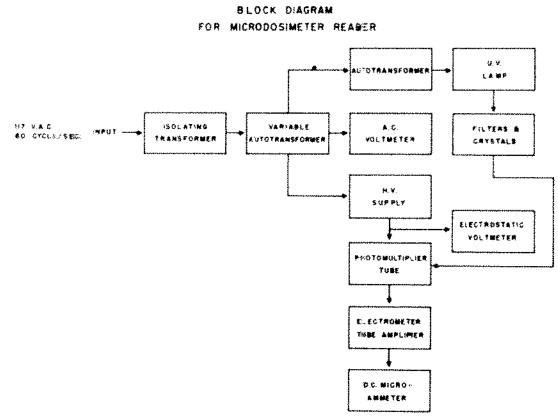

Fig. 2. Block diagram of microdosimeter reader.

to record either a major or important component of the radiation field being measured. To permit recording of lower energy gamma or roentgen rays, a series of small holes or portals was drilled into the shield wall. Number 80 drill bits were employed. Four to forty portal areas were evaluated with varying wall thicknesses and a definite correlation was found between the portal area and the surface-to-depth response.

The final design indicates that the gold wall thickness for the regular glass needle should be 17 mils while for the low Z glass

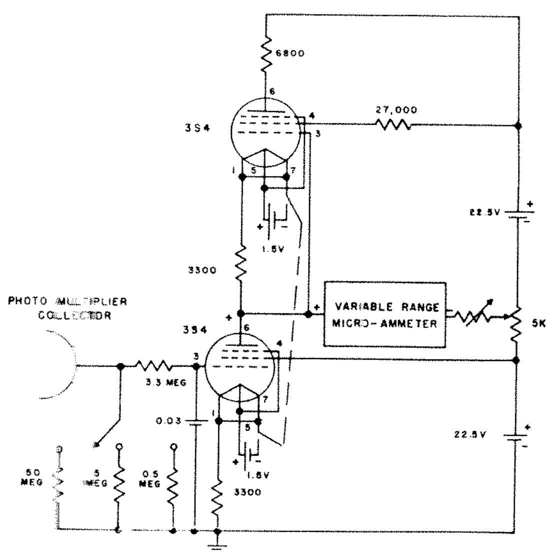

Fig. 3. Balanced bridge electrometer amplifier. Three range selector switch allows a wide range of readings.

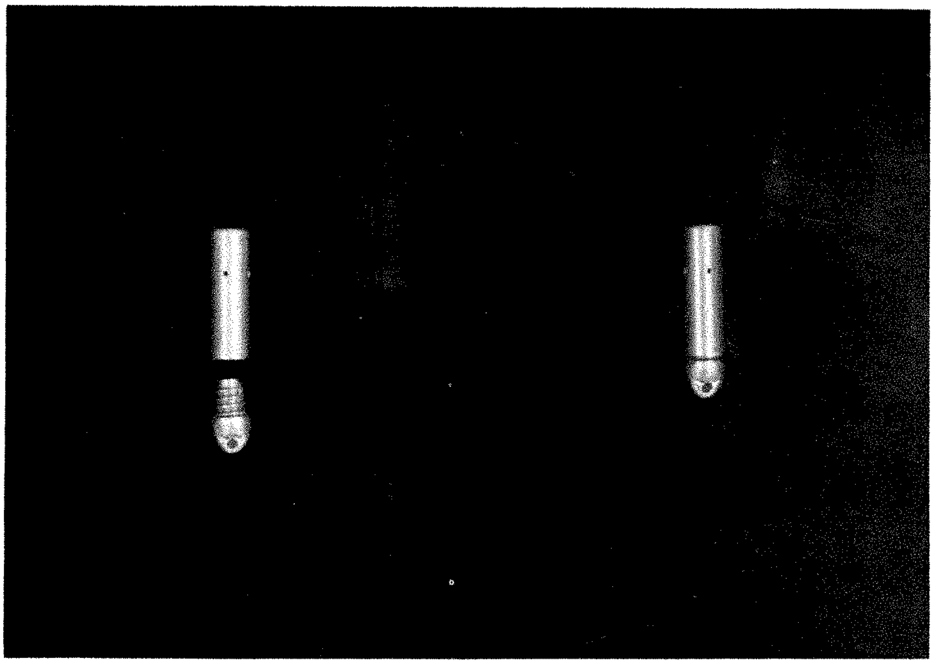

Fig. 4. Prototype of final gold shield to correct for energy dependence in the photon energy range of 0.25 to 1.33 mev.

needle it should be 10 mils. With the proper wall thickness and open portal area, the dosimeter should then be energy independent over the photon energy range of 0.25 to 1.33 mev.

APPLICATIONS

Gamma ray spectroscopy. Due to the relationship between photon energy and the mass absorption cross section for a given material, any properly and differentially shielded radiation detector may serve as a spectrometer if the techniques of absorption spectroscopy are applied. Silberstein[21,22] outlined the basic mathematical techniques required for continuous roentgen-ray spectra. Bell,[3] Jones[10] and Greening[7] have published analyses of Silberstein's method. Greenfield *et al.*[6] developed a digital computer code to obtain spectral distributions from a filtration system. A set of at least seven shields of different wall thicknesses is required. Figure 5 shows a set of filters that the authors have employed. A plot of the resulting dosimeter readings against wall thickness yields a filtration curve. Use may be made of this curve to establish an empirical relationship which should, upon proper mathematical treatment, yield the spectral distribution. Use of the glass needles would appear attractive; however, before employing them certain limitations must be noted: (1) the detector must be energy independent in the energy

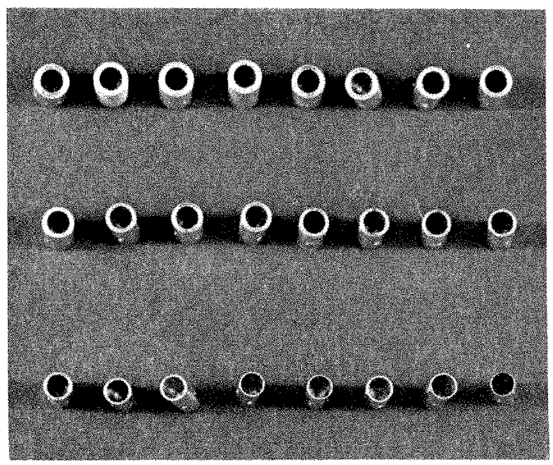

Fig. 5. A series of filters for use in absorption spectroscopy. Wall thicknesses vary from 1 mil (lower right) to 24 mils (upper left).

regions of interest, or, if it is energy dependent, this problem can be resolved by (a) suitable correction coefficients or (b) the creation of an energy independent shield; and (2) the mathematical formulation must permit analysis not only of a continuous spectrum, but also of a discrete spectrum, produced by either isotopes or neutron capture gamma rays.

Gamma neutron determinations. Kondo[11] established the relative neutron insensitivity of these needles. This has been confirmed in our studies. There is almost no response to fast neutrons and a response giving a reading of 1 r for every 5×10^9 NVT of thermal neutrons.[23] Workers at the Oak Ridge National Laboratory[23] believe the volume of the dosimeter justifies the cost of enriched Li^6 shields to eliminate thermal neutron response and permit gamma dosimetry in the presence of an intense neutron beam. One approach that might provide a more economical solution is the use of neutron shields composed of commercially available brazing material. Such alloys contain varying percentages of cadmium combined with gold and zinc or copper. While such a shield will not eliminate activation of the glass, it will reduce this to an acceptable level. The contribution of neutron capture gamma rays originating within the shield should also be insignificant. Preliminary work using bare and boron shielded dosimeters has been encouraging.

Neutron spectrometer. One other possible area of application is the use of the needle as a crude neutron spectrometer. Since the needle composition is known and an analysis of the decay spectrum is possible, the decay products can be identified and correlated with neutron energy. For instance, Na^{24} would be produced by the n, α reaction with Al^{27}. The threshold for this reaction is slightly over 8 mev., thereby indicating the presence or absence of an energetic neutron beam component. The decay of the Ag^{110} isomer could be used to measure thermal neutrons.

SUMMARY

1. The radiophotoluminescent glass dosimeter can be employed to measure radiation within the human system and a relative calibration system can be obtained for standard techniques of calibration.

2. Although the dosimeter is energy dependent for various photon energies, this factor can be eliminated in part for a specific photon range by the use of a suitable shield.

3. The use of a low Z composition glass makes possible a reduction in the wall thickness of the gold employed in the shield material.

4. The glass dosimeter can be used *in vivo* to obtain a gamma ray spectrum with the aid of accepted techniques of absorption spectroscopy. However, machine calculations are necessary due to the mathematical analysis required.

5. The glass dosimeter can be used, with a suitable lithium shield, for the measurement of gamma rays in the presence of intense neutrons.

6. The glass is being investigated for possible use in a neutron spectrometer.

7. The bare dosimeter is being investigated for total and partial absorption of various energy beta rays.

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The authors wish to express their appreciation to Dr. Schulman and Mr. Attix of the U. S. Naval Research Laboratory, and to Mr. R. Goebel and Mr. A. Ammann for their assistance in this study.

REFERENCES

The references are given at the end of Part II of this work.

IN VIVO DOSIMETRY WITH GOLD-SHEATHED MINIATURE GLASS RODS*

PART II. CLINICAL APPLICATIONS IN RADIATION THERAPY

By BERNARD ROSWIT, M.D.
BRONX, NEW YORK

IN RADIATION treatment of deep seated human cancer, there is an outstanding need for a miniature radiation detector by which to measure dosage with accuracy and with ease in all body tissues and spaces. Particularly is this so today when high energy and nuclear sources have become widely available for more radical cancer therapy—with greater risk to critical normal structures. It is generally agreed that radiation measurements within the body are far more dependable than calculations or phantom values. With this objective we surveyed existing detector systems, such as air-cavity units, Geiger-Müller counters and scintillation crystals. We could find no single instrument which fully satisfied our criteria for an "ideal" *in vivo* dosimeter for routine clinical use (Table I).

Table I

CRITERIA FOR AN "IDEAL" IN VIVO DOSIMETER

1. Miniature size (about 1×10 mm.)
2. Reasonable clinical accuracy (within ±10 per cent)
3. Wide therapeutic dose range (from 50 r to 10,000 r)
4. Freedom from electrical shock hazard (no cables)
5. Stability under rugged clinical conditions
6. Applicability in multiple units for homogeneity studies
7. Easy identification within the body and upon removal
8. Integration of repeated daily exposures (up to 10,000 r cumulative dose)
9. Independence of beam direction within the body
10. Temperature and humidity independence at reasonable levels
11. Independence of dose rate variations
12. Nontoxic to human tissues
13. Unaffected by human secretions or excretions
14. Permanent dose recording in detector, for future reference
15. Re-usable—after simple processing
16. Energy independence in the entire spectrum of therapeutic radiation now utilized for treatment of deep seated cancer
17. Correct reading in the whole range of energies most likely to be encountered within the body, regardless of portal size or depth in tissue
18. Reproducibility of response
19. Unaffected by reading procedure (no discharge of fluorescence)
20. Easy sterilization
21. Minimal cost

I. THE UNSHIELDED RADIOPHOTOLUMINESCENT GLASS ROD

A. PHYSICAL CHARACTERISTICS

A tiny photoluminescent glass rod originated by Schulman and his associates[19,20] appeared to offer the most fruitful possibilities as a practical clinical dosimeter. Its physical characteristics have been described by these investigstors, by our own group,[1,2,12,14,17] and by others.[4,5,8,11] Part I of our study deals in detail with this development in our laboratory (see preceding article).

Briefly, the dosimeter consists of a cylindrical rod of silver-activated glass containing potassium, barium, aluminum and phosphate. It measures 1 mm. in diameter by 6 mm. in length.

Under irradiation, the positive silver ions are converted to stable silver atoms through capture of electrons ejected from the glass. When subjected to an ultraviolet light in an appropriate "reader," the silver atoms (luminescent centers) produce an orange-yellow fluorescence. A photomultiplier system in the reader converts this fluorescence into an electrical current recorded in microamperes and read as roentgens. The effect is directly propor-

* From the Department of Radiation Therapy, Veterans Administration Hospital, Bronx, New York. Presented at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960.

tional, in a linear fashion, to the radiation absorbed by the glass.

Standard glass rods of known exposure (fluorescence) are employed to "zero in" the reader system prior to use and serve to check the stability of the equipment during use. Inasmuch as some fluorescence occurs during manufacture, it is necessary to secure a pre-dose reading before each exposure, later to be subtracted from the gross fluorescence.

B. ADVANTAGES

In our clinical and laboratory experience of more than three years, the glass rods appeared to offer unique advantages over more conventional dosimeters. They were of optimum size and shape and provided an accuracy of ±1–2 per cent under experimental conditions, with variations of ±5–10 per cent in limited clinical settings. They required no electrical cables or light-pipe systems within the body and could be freely employed in multiple units. Directional independence was noted in the body and in phantoms, but not in air. No corrections were needed for temperature and humidity changes during routine clinical exposure. Cumulative dose readings as high as 10,000 r and as low as 50 r were recorded with reproducible accuracy from rod to rod with single or cumulative exposures. The dose record was permanent (up to three years thus far) until erased by a simple heating procedure. The dose recording was unaffected by repeated exposure to the mercury lamp in the reader and was observed to be dose-rate independent.

Of the greatest interest was the absence of energy dependence in the high energy therapeutic range (1–2 mv., cobalt 60, cesium 137, iridium 192, radium and radon). While a commercial reader is presently available,* a "do-it-yourself" model can be fabricated for about six hundred dollars. The glass rods may be secured from a commercial source* at minimal cost (less than fifty cents each) and re-used after heating.

* Bausch & Lomb Optical Co., 730 Fifth Ave., New York, New York.

C. DISADVANTAGES

We observed a striking energy dependence of the bare glass below the supervoltage range. These values are not linear and may vary by as much as ±20 per cent from the delivered dose. We noted markedly increased sensitivity to softer, scattered radiation with portals greater than 150 cm.[2] and tissue depths greater than 8 cm. These are sharp limitations indeed to effective use of any dosimeter in radiation therapy practice.

Chipping, cracking and breaking of the glass results in reflection and refraction of these defects and false values. With reasonable care, however, the latter has not been a problem in our clinic. Although nontoxic to human tissues, the bare glass develops false fluorescence through contamination with body fluids and secretions. While plastic tubing can overcome this difficulty, it remains impossible to identify the position of the rods within the body because glass and plastic are both radiolucent. To compare the dosimeter reading with calculated or phantom values for tissue or tumor dose (Table II), one must obviously establish the precise geometric position of each dosimeter in the body and identify each unit when removed for reading.

After radiation exposure, reading should be delayed to permit complete readjustment of the internal glass structure in order to achieve the highest reading accuracy. For 90 per cent of the final reading one should wait two hours; four hours for 95 per cent values; and twenty-four hours for approximately 100 per cent or "true" reading

II. THE GOLD-SHIELDED PHOTOLUMINESCENT GLASS ROD

A. TECHNICAL DEVELOPMENT

It appeared to us that most of the important shortcomings of the bare glass rod, particularly the problems of energy dependence, identification, contamination and damage, could be overcome by development of a filter, shield, cartridge or sheath,

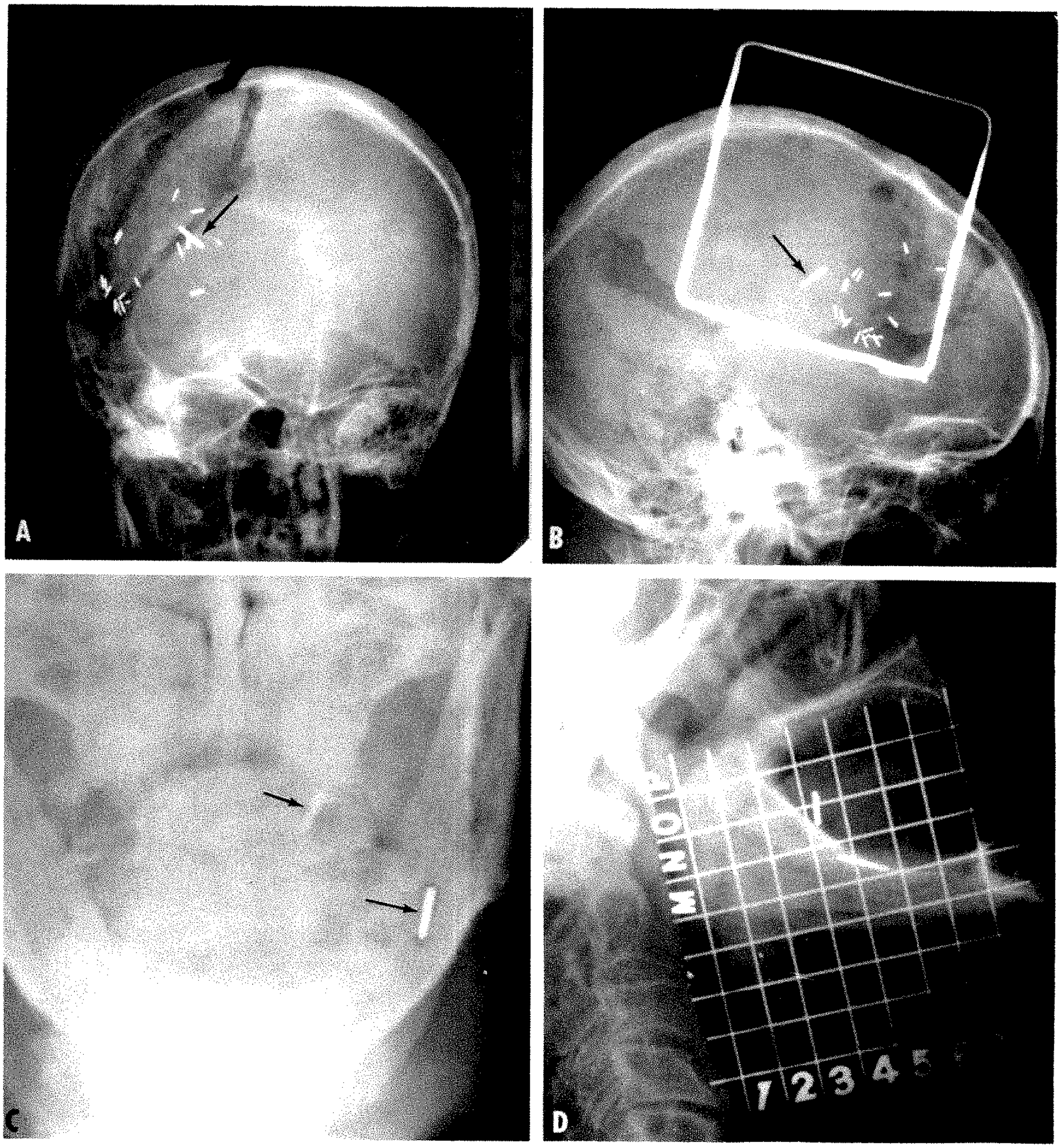


FIG. 1. (*A*) The microdosimeter is visualized here in the brain of a young man with a nonresectable glioblastoma. It was lodged in the body of the tumor in a No. 8 French polyvinyl catheter during the exploratory craniotomy (courtesy Dr. Eric Krueger). The tiny metal clips mark the several extensions of the neoplasm into contiguous normal brain tissue. (*B*) In this lateral view of the patient shown in *A*, the gold capsule carrying the dosimeter is clearly seen, oriented within a lead-solder outline of the treatment portal, ready for the first exposure. After the third exposure, the catheter with its dosimeter was withdrawn and the reading compared with a phantom value. There was an excellent correlation. (*C*) In this patient, with a massive carcinoma of the tongue, it was of interest to compare readings in the tumor and the mandible at orthovoltage (260 kv.) and at cobalt 60 energy levels. One dosimeter may be seen in the tumor and another in a drill hole in the mandible. (*D*) Lateral view of the arrangement of dosimeters shown in *C*, utilizing a metal grid to outline the portal and to orient the position of the detectors. This study is to be extended to secure ample data on absorption in bone at various energy levels. (*E*) This huge defect is the result of several futile surgical attempts to control an invasive carcinoma of the left maxillary sinus. Orthovoltage

→

TABLE II

A CROSS-SECTION OF REPRESENTATIVE CASES FOR COMPARISON OF THE RECORDED DOSIMETER VALUES AND CALCULATED OR PHANTOM DOSE

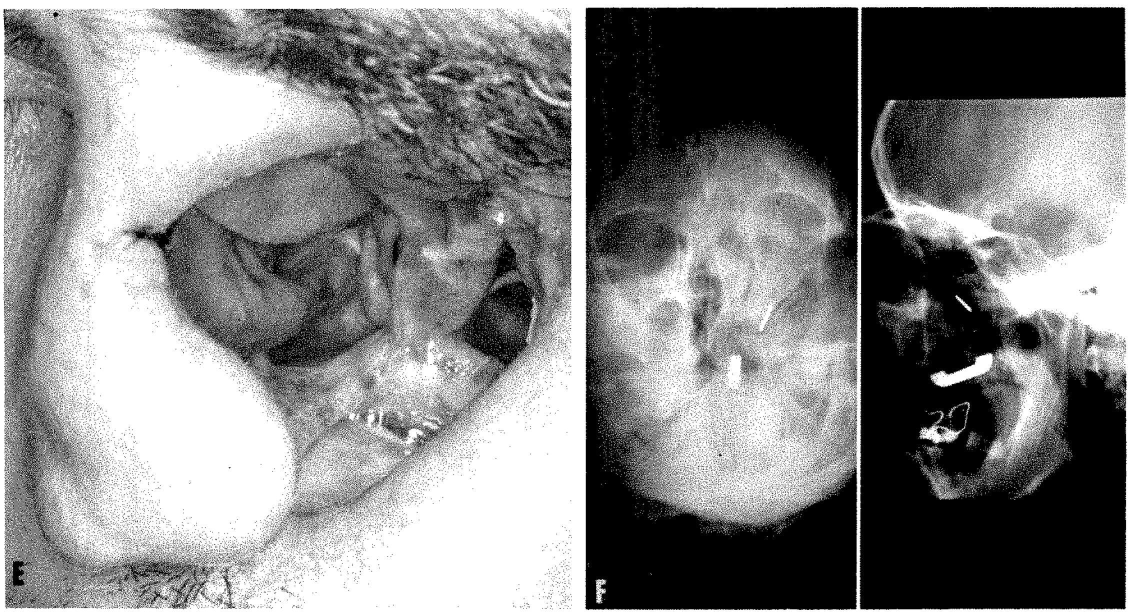
Case No.	Site	Treatment Modality	Dosimeter Value (r)	Calculated Value (r)	Per Cent Deviation
1. (Fig. 1, *E* and *F*)	Antrum	Co^{60}	211	2.1	−4.7
2. (Fig. 2*F*)	Bladder	Ir^{192}	4,200	4,000	+5.0
3. (Fig. 2*B*)	Neck	Co^{60}	286	273	+4.8
4. (Fig. 2*D*)	Cervix	Ra	990	960	+3.1
5. (Fig. 2*E*)	Chest Wall	Ir^{192}	1,877	1,832	+2.5
6. (Fig. 3, *A* and *B*)	Bronchus	Co^{60}	248	239*	+3.7
7.	Face	260 kv.	200	192	+4.2
8.	Breast	1 mv.	210	200	+5.0
9.	Kidney	1 mv.	140	138	+1.5
10.	Bladder	1 mv.	170	176	−3.4
11.	Kidney	Co^{60}	76	80	−5.0
12.	Rectum	Ra	520	540	−3.7
13.	Neck	260 kv.	200	192	+4.2
14.	Stomach	Co^{60}	200	200	0

* Dose corrected for inhomogeneity (see legend for Figure 3*B*).

fabricated from an appropriate metal of optimum thickness and especially designed for clinical use. This development in our laboratory has been adequately described in Part 1 of this report (preceding article).

The final product was a tiny cartridge of gold, 1.6 mm.×10 mm., easily cut from gold tubing of 10 mils wall thickness and a lumen of approximately 1.02 mm. diame-

(*Text continued on page 579*)



treatment to 6,000 r also proved ineffectual. It became imperative to determine with accuracy all additional dosage if we were to utilize safely the cobalt 60 beam and intracavitary radium implants. (*F*) Same patient as in *E*. Microdosimeters were attached to an acrylic mold, which was fabricated to fill the defect in the patient's skull. In a "verification" procedure, employing the cobalt 60 beam, the glass rod recorded a dose which varied by only 4.7 per cent from the intended or phantom value.


A
C
D

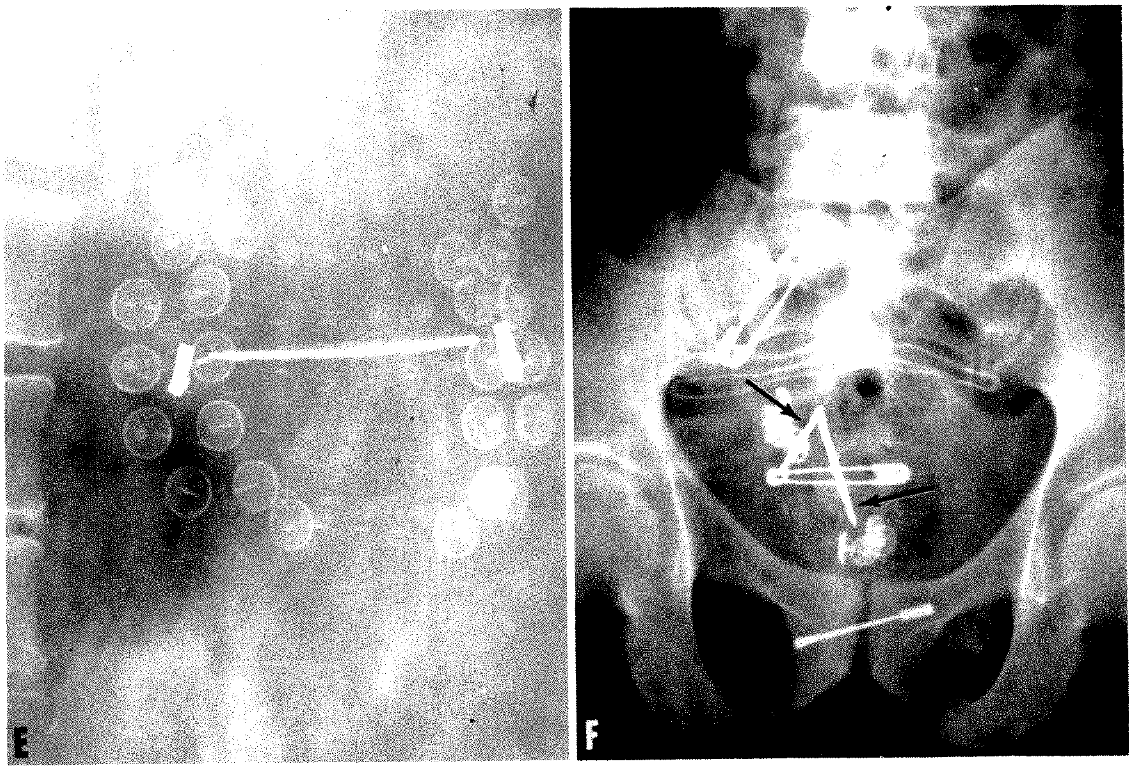


Fig. 2. (*A*) Note this huge recurrent carcinoma in the left neck of a patient recently operated upon for carcinoma of the larynx. The striking variation in the contour of this ulcerating and exophytic tumor made precise dosage calculation difficult. (*B*) Same patient as in *A*. A glass rod in a hollow radium needle has been implanted in the tumor to provide accurate *in vivo* dosage measurement. The measured value proved to be within 5 per cent of the calculated dose, using the cobalt 60 teletherapy beam. (*C*) Note the three microdosimeters in tandem in a No. 8 French polyvinyl feeding catheter, to monitor rotational therapy for esophageal carcinoma. The measured dose in the 1,000 kv beam was within less than 5 per cent of the phantom value at all three dosimeter levels. (*D*) Pelvic roentgenogram illustrates a unique attempt to measure radium dosage at point B in the left parametrium of a patient receiving treatment for cervical carcinoma (courtesy Dr. Gray Twombly). Note the 4 cm. hollow radium needle (containing glass rods) implanted at point B through the patient's vagina (left lateral fornix). We intended to deliver 1,000 r to this site in each of 2 successive implants. The recorded dose was 900 r while the calculated dose (through analytical geometry) was exactly 960 r. Note another needle in a catheter in the bladder, carrying its dosimeter load. Rectal dosimeters have been similarly employed in our Radiation Clinic. Further, dosage at point A can be easily acquired by means of interstitial rod implant or by a catheter (with rod) in the ureter. (*E*) This roentgenogram shows a two-plane, iridium 192 seed implant (in nylon thread) in a large metastatic carcinoma on the chest wall. Four dosimeters, mounted in individual gold shields, have been placed in tandem, in a plastic tube, through the midplane of the implant. The recorded values varied by only 2.4 per cent from the calculated dose. (*F*) A patient with carcinoma of the bladder at the trigone required a single plane iridium 192 implant for a planned tumor dose of [illegible],000 r in six days. One hollow radium needle containing a dosimeter was placed directly in the center of the implant and withdrawn on the fourth day as a monitoring maneuver. The dosimeter read 4,200 r, compared with a calculated dose of 4,000 r, a variation of only 5 per cent. This variation can be accounted for by the curvature in the bladder, whereas the dose calculations were based on the Paterson-Parker figures for a flat or planar implant. A second needle with dosimeter is seen at the periphery of the implant.

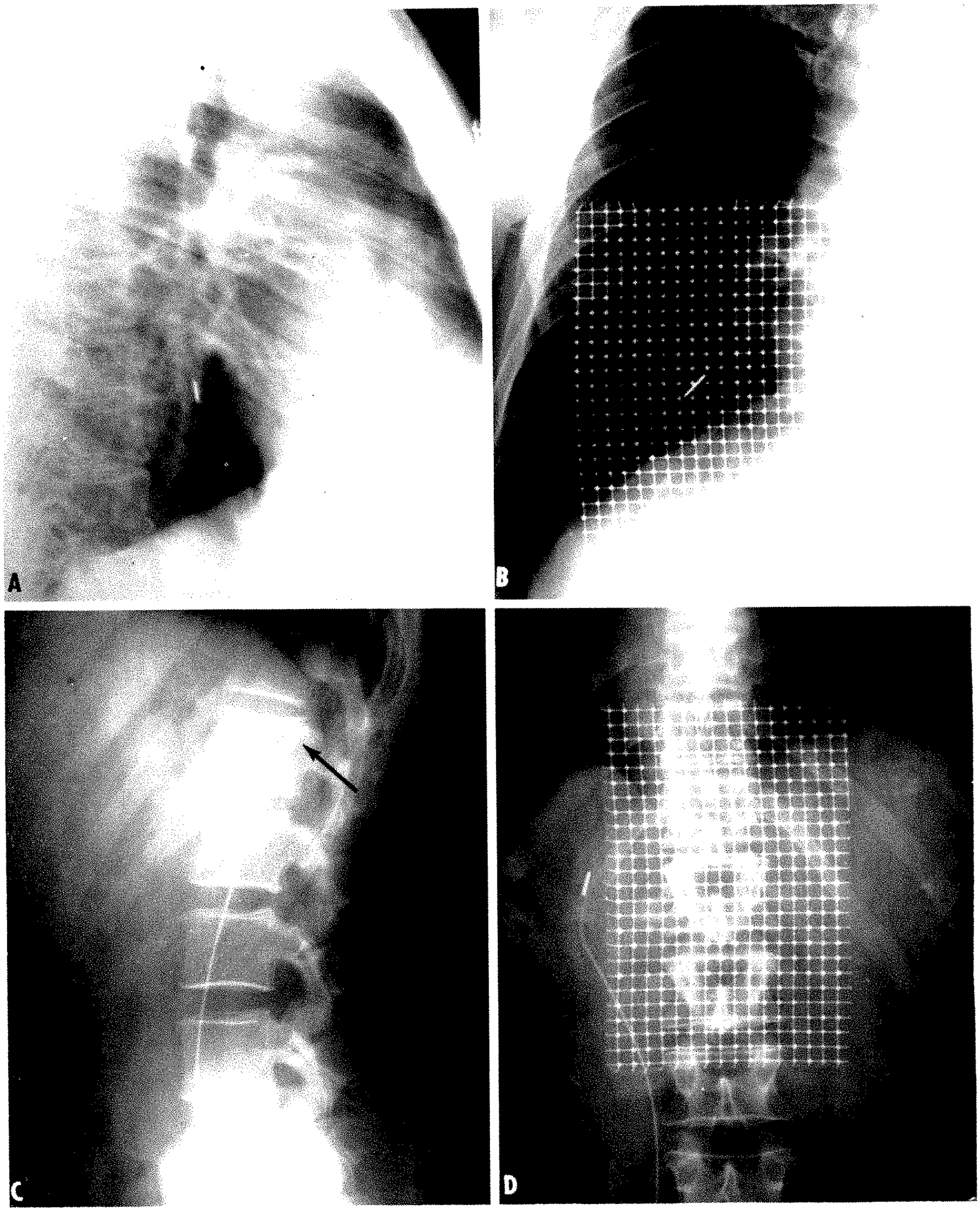


Fig. 3. (*A*) In this lateral chest roentgenogram is shown a gold-shielded dosimeter in a plastic tube, lying within the right lower lobe bronchus of an individual with a normal right lung. With this system, we are studying the inhomogeneity factor, so important in the radiation treatment of intrathoracic neoplasms. (*B*) Same patient as in *A*. The wire grid serves to outline the treatment portal as well as to orient the detector in the beam. A lateral roentgenogram is also made in this manner. The measured dose from the cobalt 60 exposure was 248 r. The corrected calculation was 239 r, a variation of only 3.7 per cent (reference to inhomogeneity correction tables of Jacobson suggested a correction value of 15 per cent[9]). A study of

ter. One end was sealed and the other carried a tiny screw cap. After many trials a system was evolved to permit entry of an optimum level of scattered radiation; four tiny holes, each at 90° from the other, were drilled in the midsection of the shaft. For ready identification, each gold cartridge was engraved in an orderly numbered system.

B. SPECIAL ADVANTAGES

With the gold-shielded glass rod we achieved:

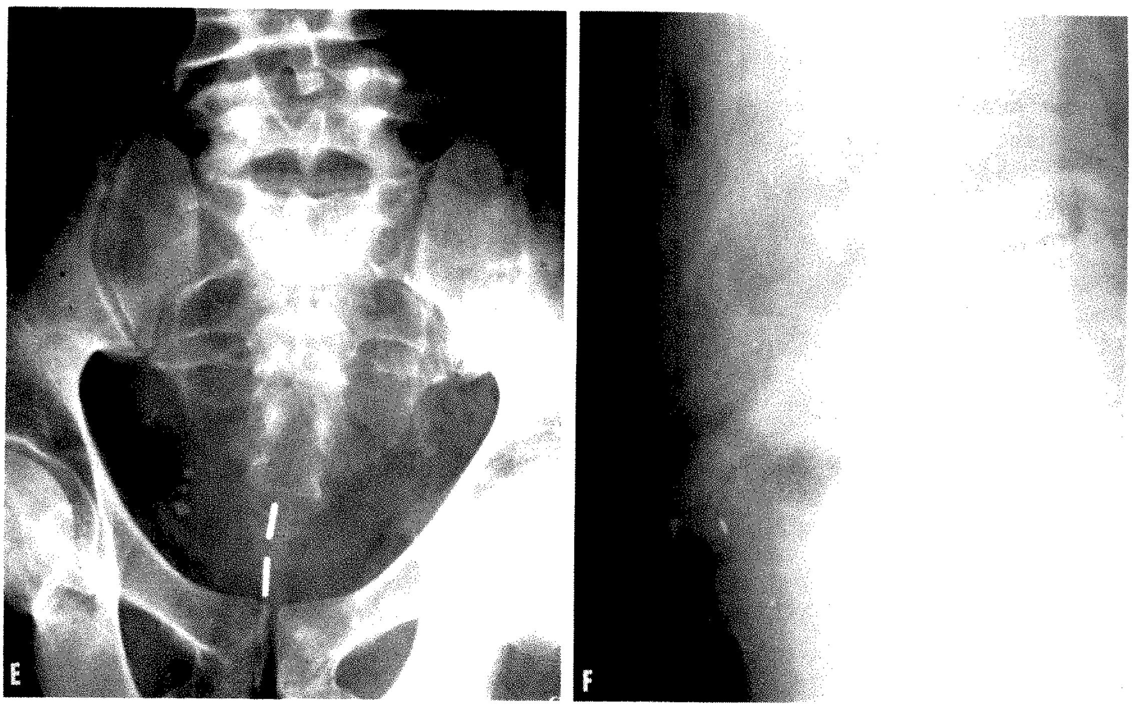
1. Independence of therapeutic energy or modality employed—from 250 kv. to 2,000 kv., including radium, radon, cobalt 60, cesium 137, iridium 192 and other high energy sources. Therapy with different modalities can thus be measured (and added) in the same patient in the same lesion, with confidence in the values. This eliminates the requirement of calibrating a dosimeter against each specific therapy source.

2. Independence of portal size—from the smallest to the largest used in clinical practice including total body exposure.

3. Independence of depth in tumor or tissue—from the skin to 20 cm.

4. Reduction in probability for contamination and of damage of glass rods.

5. Easy identification by means of roentgenography and by engraved numbers.



the lung inhomogeneity problem has been initiated. (*C*) A dosimeter was successfully placed within this patient's renal pelvis, using a No. 8 French polyvinyl catheter, stiffened with a slender conventional urethral catheter. The urine drained well while radiation therapy was administered. (*D*) The grid wire represents the uppermost portal employed in the postoperative cobalt 60 irradiation of this patient's para-aortic lymph nodes after removal of a testicular seminoma. It is of interest that the dose measured at the renal pelvis was only 15 per cent of the tumor dose in the central axis of the beam. The study of renal dosage is being extended. (*E*) This patient is to receive radiation treatment for cancer of the bladder using the cobalt 60 rotational beam. A pair of dosimeters in their gold capsules has been inserted via urethral catheter for precise recording of the tumor dose. (*F*) In this patient with an advanced carcinoma of the bladder, a microdosimeter has been placed within the abdominal aorta via the femoral artery in an attempt to secure a recording of the dose delivered to the para-aortic lymph nodes.

6. Increased useful range of dosimeter—from 50 r to 20,000 r.

7. Economical use (completely fabricated gold cartridges cost about three dollars each).

8. Nontoxicity in human tissues—even after protracted implantation periods for cumulative dose records.

9. Miniaturization to a point wherein nearly all body spaces and tissues are pregnable to dose recording.

10. Accuracy with variations of only ± 5 per cent clinically and ± 1–2 per cent experimentally.

C. DISADVANTAGES

There appeared to be no significant deficiencies of the gold-shielded glass rod system.

III. CLINICAL TRIALS

We have employed the gold-shielded microdosimeter in 40 patients receiving radiation therapy for various malignant diseases, including carcinoma of the kidney, testicle, larynx, tongue, stomach, antrum, breast, brain, cervix, vagina, esophagus and bladder, soft tissue sarcoma and malignant lymphoma.

Nearly all body tissues and spaces were entered with relative ease for *in vivo* dose recording, including the ureter, renal pelvis, parametrium, mandible, nasopharynx, paranasal sinuses, trachea, bronchus, brain, stomach, bowel, bladder, uterus, heart, mediastinum, aorta and the general vascular tree.

The detectors were stationed singly and in multiples in (a) primary tumors, (b) regional lymph nodes, (c) distant metastases and (d) nearly all normal structures in the path of the therapy beam. In these stations they were employed interstitially, intravascularly, intracavitarily and on the surface, for dose verification and surveillance. After exposure to radiation, the glass rods were removed from their gold shields and placed in the reader.

Conventional and easily available devices were utilized to carry the shielded dosimeters, such as plastic tubing, hollow radium needles, Foley catheters, Friedman-Lewis catheters, Miller-Abbott tubes, cardiac catheters, etc. One of the most generally useful devices was a simple polyvinyl feeding tube, No. 8 French, costing less than fifty cents. With one or more cartridges tucked into its tip, we have been able to enter the ureters, renal pelvis, uterus, bronchial tree, blood vessels and other important structures hitherto inaccessible to a radiation dosimeter.

The treatment modalities used in this study included orthovoltage (260 kv.), supervoltage (1 mv.), cobalt 60 teletherapy, interstitial radium, radon, and iridium 192. In this energy range, complete linearity and energy independence was observed, regardless of portal size and depth in the body up to 20 cm. Portals up to 600 cm.^{2} were used. Even when several treatment modalities were employed for the same tumor, the dosimeter summated fractionated doses, with variations of less than ± 5 per cent from the calculated or phantom value.

Contamination of the glass and damage to its structure are now rarely encountered in our clinic. The bare glass is gently handled with tiny tweezers and placed in the protective gold shield without difficulty. The x-ray technician takes charge of the loading and unloading, and the preparation and sterilization of needles, catheters and other devices. Cold sterilization (using zephiran) is invariably employed because excessive heat will affect the glass.

IV. WORK IN PROGRESS

The gold-shielded glass microdosimeter is presently being employed in living human subjects for special investigations such as evaluation of: (1) new treatment planning techniques; (2) assessment of methods for precise beam orientation and patient immobilization; (3) inhomogeneity factors in lung and bone at various energy levels; (4) recording tissue dose in critical normal structures in conventional and experimental treatment plans; (5) dose verification procedures in individual patients under

treatment; (6) dependability of the microdosimeter with use of energy levels up to 100 mv. roentgen rays, high energy electron beams, and a broad spectrum of radioactive isotopes; (7) evaluation of techniques for more effective total body irradiation at high dose levels plus marrow transplants, in patients with advanced malignant disease; and (8) efficiency of the glass microdosimeter in a mixed neutron-gamma beam, a problem of major interest for those planning neutron irradiation for tumors of the brain.

CONCLUSIONS

1. We have developed a practicable and reliable microdosimeter system for accurate *in vivo* human dosimetry in radiation therapy.
2. This system is immediately adaptable to routine clinical use and experimental studies.
3. It has been employed successfully in nearly all body tissues and spaces in cancer patients receiving ionizing radiation.
4. The detectors consist of tiny photoluminescent glass cylinders enclosed in miniature gold cartridges which can be easily and quickly fabricated.

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Bronx 68, New York

For their assistance in this investigation, we wish to thank Drs. Schulman and Attix of the U.S. Naval Research Laboratory, Dr. Max Pleasure, Chief of our Dental Service, and Mr. Louis Maddalone, Mold Technologist in our Radiation Clinic.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

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Forty-third Annual Meeting: Broadmoor Hotel, Colorado Springs, Colo., May 10–14, 1961.

* *Ex officio.*

EDITORIALS

FORTY-THIRD ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE American Radium Society was organized forty-five years ago, in June, 1916, during an Annual Meeting of the American Medical Association, by 24 physicians interested in radium therapy, under the leadership of W. H. B. Aikens of Toronto, Canada, acting as temporary president, and R. E. Loucks of Detroit, Michigan, as the temporary secretary. H. K. Pancoast, M.D., was in charge of the dinner and Henry Schmitz, M.D., of Chicago, chairmanned a Committee on Constitution and Bylaws. The name chosen was "The American Radium Society."

The object of the Society was, and still is, "to promote the scientific study of radium and other sources of ionizing radiation in relation to their physical properties and their therapeutic application" and to maintain the high ethical standard among those using these agents for treatment.

The Forty-Third Annual Meeting (during World War II some meetings were omitted) will be held at the Broadmoor Hotel in Colorado Springs, Colorado, on Wednesday through Saturday, 10, 11, 12, and 13 May, 1961.

On Wednesday, 10 May, 1961, the Executive Committee will meet and in the afternoon there will be general registration.

The first Executive Business Session will be held during a breakfast meeting for members of the Society on Thursday morning, 11 May. At 9:00 A.M. the Scientific Program opens with an Address on "The Concept of a Cure" by Dr. Fred C. D. Collier, Professor of Surgical Pathology, University of Alabama Medical School, Birmingham, Alabama. Dr. Collier will be introduced by Dr. Luther W. Brady, Jr., Chief of the Radiotherapy Division of The Hahnemann Medical College and Hospital of Philadelphia. Dr. Collier's Address will set the tone and provide the Keynote of the Meeting.

A critical survey of the current methods of treatment and results obtained in carcinoma of the ovary and brain tumors will highlight the program, and some new aspects of the physics of radiation therapy as well as newer ideas of treatment will be presented.

The Janeway Lecture will be delivered by a prominent Canadian neighbor and member of the Society, Dr. Clifford L. Ash, Director of the Ontario Cancer Institute at Toronto incorporating the Princess Margaret Hospital, and Professor of Radiotherapy at the University of Toronto..Dr. Ash's address, which is most timely, is entitled "Intra-Oral Cancer, a Twenty-five Year Study."

A Social Hour will be held on Thursday evening sponsored by the Radium Chemical Company. On Friday evening, there will be a reception, followed by the Annual Banquet. The past presidents of the American Radium Society will be honored with ceremonies and "high jinks" at a special table during this banquet. The Koshare Indians will give a series of colorful tribal pageants and dances after the banquet.

Three distinguished French colleagues will participate in the program. Professor A. Lacassagne, one of the earliest investigators in the field of radiobiology, will discuss new experimental work on carcinoma of the liver. Dr. A. Ennuyer and Dr. Bernard Pierquin of the Fondation Curie, Paris, France, will deal with topics, the titles of which will be announced in the final program.

Colorado Springs is particularly beautiful in the spring month of May. The charming old Broadmoor Hotel is nestled beside a lake in the foothills of the Rocky Mountains. Pike's Peak, with an altitude of 6,500 feet, is within sight to the north and the Air Force Academy is located in the foothills.

The Broadmoor is modernized in every way. A new auditorium with a parabolic roof meets every requirement for a convention. The charm, services and facilities of the hotel ensure a very pleasant visit. Boating, water skiing, a heated swimming pool and an indoor ice rink give opportunities for varied recreation. On any afternoon an organized scenic tour through the mountains and valleys can be arranged.

Registration will begin on Wednesday, 10 May, from 2:00 P.M. to 5:00 P.M. and will continue throughout the duration of the meeting.

You are urged to make hotel reservations through Dr. Juan A. del Regato early, since the list will be closed 15 April, 1961. Accommodations at motor courts and other hotels may be requested as well.

The officers of the American Radium Society cordially invite you and urge you to attend its Forty-third Annual Meeting in the beautiful surroundings of the Broadmoor Hotel in the foothills of the Rocky Mountains.

Jesshill Love, M.D., *President*
The American Radium Society
Memorial Cancer Foundation
235 Bath Street
Santa Barbara, California

WILLIAM STELL NEWCOMET
1872–1960

WITH the passing of William Stell Newcomet on September 9, 1960, Radiology lost another distinguished pioneer.

Born in Philadelphia, Pennsylvania, on July 20, 1872, the son of Henry Walborn Newcomet and Elizabeth Kesia Stell, Dr. Newcomet received his primary education in the schools of Philadelphia. He attended Friends' Girard Avenue School and the Lauderbach Academy. At the age of thirteen, following his father's early death, his mother decided to take her three children to Europe. While there, William New-

comet enrolled at the University of Berlin (1888–1889) and remained after his family returned home. His major interest was in chemistry. The instructions that he received in German and in chemistry were to be of great value to him in his medical career. In 1890, he returned to Philadelphia and matriculated at the Medical School of the University of Pennsylvania, from which he received his M.D. degree in 1893. After an internship at St. Agnes Hospital in Philadelphia, he entered general practice and became associated with the St. Agnes Hospital and the Rush Hospital for Consumption. He was also the attending physician to the House of the Good Shepherd.

At the Rush Hospital, in 1898, Dr. Newcomet became interested in the employment of x-rays in the study of the chest, and in 1899, he became the director of the X-Ray Department of the Presbyterian Hospital in Philadelphia, a position he held for approximately fifty years.

In 1904 the Oncologic Hospital of Philadelphia was organized and Dr. Newcomet was placed in charge of the X-Ray Department. Shortly thereafter, in 1907, radium was acquired for the first time in that institution. Dr. Newcomet constructed the radon apparatus in this institution in 1921.

In 1916, Dr. Newcomet joined the Red Cross unit of the Presbyterian Hospital and entered the Army as First Lieutenant on June 15, 1917. From this period until 1919, he served at Camp Greenleaf and Camp Gordon in Georgia, as Acting Adjutant in charge of the X-Ray Department, Instructor in the Rules of the Army Survey and Court Officer. From February, 1919, to April 29, 1919, he was in charge of the X-Ray Department at General Hospital, No. 35, West Baden, Indiana, when he retired as a Major. He was advanced to a Lieutenant Colonel in the Reserve Corps in 1920.

Dr. Newcomet was primarily interested in organized medicine and found time to actively participate in many organizations. His affiliations included: The Philadelphia County Medical Society, Vice President and Member of the Board of Directors for eleven years; Fellow of the College of Physicians of Philadelphia; President, West Branch Philadelphia County Society, 1917; Fourth Vice President, American Roentgen Ray Society, 1909; Secretary of American Radium Society and its President in 1925; Fellow of the College of Radiology; Diplomate of the American Board of Radiology; Member of the Franklin Institute (1944–1960); Member of the American and Philadelphia Mineralogical Societies; and an active and devoted Mason and Past Master in the Stephen Girard Lodge 450, Pennsylvania.

Dr. Newcomet was well known to earlier generations of radiologists. He was a quiet and gentle physician with a good sense of humor and was liked by everyone. His ideals were on a high plane. His knowledge of physics and chemistry provided the background for much of his early work in radium and roentgen therapy. He was well informed on the world's literature and generously contributed to it.

His publications on chest diseases date back to 1899. His contributions on "Treatment of Malignant Disease with X-Rays," in 1903; "Pathological Changes in Tissue under the Influence of the X-Rays" and his book, "Radium and Radiotherapy," published by Lea and Febiger in 1914, have stood the test of time, and many of the observations are in accord with current thinking. Dr. Newcomet's greatest interest probably was in therapy, especially with the use of radium, and he developed a well earned reputation for his work with the care of hemangiomas in children. It should be stated that Dr. Newcomet was one of the very few pioneers who was most cautious and, so far as I know, did not develop any radiation damage changes on his hands, face and/or body.

Dr. Newcomet came from a Pennsylvania-German background. He believed in thrift and in using one's time well. His profession was his chief interest and he rarely took vacations. He had several

hobbies from which he derived great enjoyment. Dr. and Mrs. Newcomet spent many happy hours along the Brandywine, while he sketched that lovely stream. From childhood he was an avid collector of minerals and as he grew older he made trips to many mines and caves to obtain new specimens for his large collection. He was particularly interested in fluorescent minerals and exhibited them under various lights. His hobby of keeping bees on occasion presented problems in his city home when they would swarm and leave for greener pastures.

On April 22, 1897, Dr. Newcomet married Katherine E. Mackeown. His daughter, Mrs. Paul W. Sutro and three grandchildren, survive.

The onset of Dr. Newcomet's terminal illness stemmed from metastatic lesions in the chest secondary to a carcinoma of the colon which had been removed eighteen months before. Death ended the career of a man whose life had been one of achievement and enrichment for himself, his profession and for those who were privileged to know him.

EUGENE P. PENDERGRASS, M.D.

THE AMERICAN RADIUM SOCIETY

TENTATIVE PROGRAM

The following is the tentative program arranged by the Program Committee for the Forty-third Annual Meeting of the American Radium Society to be held at the Broadmoor Hotel, Colorado Springs, Colorado, Wednesday through Saturday, 10, 11, 12 and 13 May, 1961.

Wednesday, 10 May, 1961

9:00 A.M.–4:00 P.M.
Executive Committee Meeting.

2:00–5:00 P.M.
Registration.

Thursday, 11 May, 1961

7:30 A.M.
First Executive breakfast Business Session for members.
Appointment of committees, election of new members.

9:00 A.M. Onward.
Registration

9:00 A.M.
First Scientific Session.
Robert L. Brown, M.D., Chairman.

Opening Ceremonies and Welcome Address. Jesshill Love, M.D., Santa Barbara, California.

Keynote of the Meeting: Concept of a Cure. Fred C. D. Collier, M.D. (by invitation), Birmingham, Alabama.
Introduction of Dr. Collier by Luther W. Brady, Jr., M.D., Philadelphia, Pennsylvania.

Comparative Study of Supervoltage Radiotherapy Techniques in Some Pelvic Malignancies. Jose Noriega, M.D., Mexico City, Mexico.

Panel Discussion

A Critical Analysis of Current Therapy of Carcinoma of the Ovary: Natural history of ovarian neoplasms. Is surgery alone adequate? Has postoperative irradiation proven itself? Value of radioisotopes and chemotherapy.
Philip Rubin, M.D., Rochester, N. Y., Moderator.

Panelists: Malcolm B. Dockerty, M.D. (by invitation), Rochester, Minnesota, John G. Masterson, M.D. (by invitation), Brooklyn, New York, Howard B. Latourette, M.D., Iowa City, Iowa, Vera M. Dalley, M.D. (by invitation), London, England, and others.

The Influence of the Time Factor on the Dose Response Curve. Lucille A. DuSault, A.B., Detroit, Michigan.

Observations of Radioresponse of some "Radioresistant" Neoplasms. Franz J. Buschke, M.D., San Francisco, California.

12:15 P.M.
Recess.

12:30 P.M.
Luncheon for members, guests and wives.
T. Christen, the First Investigator of the HVL. Speaker, E. Dale Trout, B.S., Sc.D., Milwaukee, Wisconsin.

2:00 P.M.
Victor Marcial, M.D., Chairman.

Symposium

Radiosensitivity and Radiocurability Judged by Microscopical Techniques.
Joseph L. Morton, M.D., Moderator.

The Cytologic Prognosis in Cancer of the Cervix. Ruth M. Graham, Sc.D. (by invitation), Buffalo, New York.

Radiosensitivity Testing of Cancer of the Cervix. Saul B. Gusberg, M.D., New York, New York.

Can Radiosensitivity and Histopathology Be Correlated? Arthur T. Hertig, M.D. (by invitation), Boston, Massachusetts.

Incidence and Treatment of Radiation Necrosis of the Intraoral Cavity. William S. MacComb, M.D., Houston, Texas.

(Title to be announced.) Dr. Bernard Pierquin (by invitation), Villejuif (Seine), France.

5:30 P.M.
The Janeway Lecture. Clifford Ash, M.D., Director, Ontario Cancer Institute, Toron-

to; Professor of Radiotheraphy, University of Toronto. Intra-Oral Cancer, a Twenty-five Year Study.

6:30 P.M.
Social Hour.

7:30 P.M.
Dinner *ad libitum.*

Friday, 12 May, 1961

7:30 A.M.
Second Executive breakfast Business Session for members.
Committee reports. Old and new business. Introduction of new members. Required attendance of all new members.

9:00 A.M. Onward.
Registration.

9:00 A.M.
Second Scientific Session.
Charles Stetson, M.D., Chairman.

Ten Year Evaluation of the Treatment of Bone Metastasis from Breast and Prostate Carcinoma Using P^{32} and Testosterone. Jack G. S. Maxfield, M.D., and J. R. Maxfield, Jr., M.D., Dallas, Texas.

Complications in the High Dose Total Pelvic Irradiation of Female Pelvic Cancer. Paul M. Chau, M.D. (by invitation), Gilbert H. Fletcher, M.D., and Felix N. Rutledge, M.D. (by invitation), Houston, Texas.

The Intravenous Pyelogram and Carcinoma of the Cervix. Richard W. Stander, M.D. (by invitation), and Robert K. Rhamey, M.D. (by invitation), Indianapolis, Indiana.

Cobalt 60 Tangential Dosimetry. Harold E. Johns, Ph.D., Toronto, Ontario.

(Title to be announced.) Dr. A. Ennuyer (by invitation), Paris, France.

Hemipelvectomy in the Treatment of Advanced Cancer. Theodore R. Miller, M.D., New York, New York.

A Cesium Unit for Head and Neck Therapy. M. Lederman, M.D., London, England.

Clinical and Biological Studies of Actinomycin D and Radiation. Giulio J. D'Angio, M.D. (by invitation), Boston, Massachusetts.

Low-Level X Irradiation and the Very Early Mammalian Embryo. Roberts Rugh, M.D. (by invitation), New York, New York.

Cancer Arising Many Years after Radiation Therapy of Benign Lesions in the Cervical Region. John M. Hanford, M.D. (by invitation), and Edith H. Quimby, Sc.D.

Honored speaker of the Forty-third Annual Meeting of the American Radium Society. Experimental Carcinoma of the Liver. Professor A. Lacassagne, Paris, France.

12:15 P.M.
Recess.

2:00 P.M.
Tour of the United States Air Force Academy.

6:30 P.M.
Reception.

7:30 P.M.
Annual Banquet.
Presentation of the Janeway Medal.
Table honoring the past Presidents of the American Radium Society.
Presentation of Mementos to past Presidents.
Spectacular dance revue by the Koshare Indians.

Saturday, 13 May, 1961

9:00 A.M. Onward.
Registration.

9:00 A.M.
Third Scientific Session.
Gilbert H. Fletcher, M.D., Chairman.

Board of Inquiry. A three man board will be picked to review a series of very unusual cases. Arbitrator, Milton Friedman, M.D., New York, New York.

Radiation Therapy of Brain Tumors. Robert J. Bloor, M.D., and Arch W. Templeton, M.D. (by invitation), Rochester, New York.

Localization of Brain Tumors Using I^{131}HSA; Problems of Instrumentation and Technique. Edward B. Schlesinger, M.D. (by invitation), Sheila deBoves, M.S. (by invitation), and Juan Taveras, M.D. (by invitation), New York, New York.

Irradiation of Meningioma. Milton Friedman, M.D., New York, New York.

Should We Treat Glioblastoma Multiforme? Juan M. Taveras, M.D. (by invitation), and J. Lawrence Pool, M.D., New York, New York.

A Three Dimensional Radium Reconstruction Device. Jerome M. Vaeth, M.D., San Francisco, California.

A Moving Picture: "Radium Implantation: Operating Room Techniques." Fernando G. Bloedorn, M.D., and Carlo A. Cuccia, M.D., Baltimore, Maryland.

Distant Metastasis from Oral Cancer. Sidney Rubenfeld, M.D., New York, New York.

Why Go to the Moon? Maj. Gen. David Wade, U.S.A., Commanding Vandenberg Air Force Base, will appoint a discussant to outline the necessity for space travel and investigation.

12:30 P.M.

Third Executive Business Session.

Election of officers. Introduction of new officers.

12:45 P.M.

Luncheon *ad libitum*.

Adjournment.

Papers to be read by title:

Post Radiation Treatment of Total Body Lethal Irradiation with Cell Free Spleen Extract (Pending AEC and USN approval). Friedrich P. Ellinger, M.D., Ph.D. (by invitation), Washington, D. C.

A World Survey of Radioisotope Teletherapy Units (900 units in 50 countries) (Pending approval of the IAEA). Kia-Chi Tsien, B.Sc., M.A., Vienna, Austria.

Radiotherapy in the Luis Razetti Institute of Cancer in Caracas. Raul Vera V., M.D., Caracas, Venezuela.

Address all applications for hotel reservations or correspondence relevant to the meeting to:

Juan A. del Regato, M.D., Chairman of Arrangements
Penrose Cancer Hospital
2200 No. Cascade Avenue
Colorado Springs, Colorado

NEWS ITEMS

DAVID ANDERSON-BERRY PRIZE (1961)

A David Anderson-Berry Silver-Gilt Medal, together with a sum of money amounting to not less than one hundred pounds sterling (£100/$280.00), will be awarded in 1961 by the Council of the Royal Society of Edinburgh. The Prize will be awarded for recent work on the effects of x-rays and other forms of radiation on living tissues. Published work will be taken into consideration if submitted to the Society with the application.

In addition to direct application for the Prize, proposals may be made on behalf of others.

Applications and proposals must be in the hands of the General Secretary, Royal Society of Edinburgh, 22/24 George Street, Edinburgh 2, Scotland, not later than March 31, 1961.

COURSE IN RADIOLOGY OF THE CHEST INDIANA UNIVERSITY

The Department of Radiology of Indiana University School of Medicine announces a postgraduate course in Radiology of the Chest to be given April 6, 7, 8, and 9, 1961, at the Medical Center in Indianapolis.

The course is planned primarily for the general radiologist but is open to all physicians having an interest in this field. Presentations will consist of lectures, panel discussions, and film interpretation conferences, correlating the radiologic, pathologic, and physiologic aspects of various chest conditions encountered in clinical practice.

Guest participants include Drs. Robert P. Barden, William R. Eyler, Benjamin Felson, Melvin M. Figley, C. Allen Good, Jr., John F. Holt, Harold G. Jacobson, and Averill A. Liebow of this country, and Doctor George Simon of London, England.

The subjects for discussion have been arranged so that each day is devoted to one or two subdivisions of the field, thus facilitating a more comprehensive evaluation of lesions of similar origin, as well as those producing similar roentgen findings. Further information regarding this course may be obtained by writing the Director of Postgraduate Medical Education, Indiana University School of Medicine, Indianapolis 7, Indiana.

UNIVERSITY OF WISCONSIN POSTGRADUATE COURSE ON DISEASES OF THE CHEST

The Departments of Radiology and Pathology of the University of Wisconsin Medical School are sponsoring a Postgraduate Course dealing with Diseases of the Chest on May 11–13 inclusive. The course will consist of lectures and panel discussions covering a variety of diseases of the lungs and heart. It will be given by a panel of guest speakers, both pathologists and radiologists, together with members of the University of Wisconsin Medical School Faculty. Guest speakers include Drs. John A. Campbell, Benjamin Castleman, Jesse E. Edwards, C. A. Good, Averill A. Liebow and Eugene Van Epps. For further information write to William D. Stovall, M.D., Coordinator of Postgraduate Medical Education, University of Wisconsin Medical School, Madison 6, Wisconsin.

THIRD INTERNATIONAL CONVENTION OF X-RAY TECHNICIANS

The Third International Convention of X-Ray Technicians will meet at the Queen Elizabeth Hotel in Montreal, Quebec, Canada, June 24–29, 1961. Mr. Don Atkins, R.T., is the co-chairman of publicity for this convention.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Radio Terapia. By Giulio Tori. Pp. 693, with 351 illustrations. Prof. R. Patron, Bologna, Italy, 1960.

In the preface to this book, Prof. G. Palmieri notes that most radiology residents relegate radiation therapy to a secondary role and prefer to dedicate much more time and effort to diagnostic radiology. For those who take radiotherapy more seriously, there is a need for texts which, without overemphasis on one or the other facet of radiotherapy, encompass the whole with enough detail to give the residents a secure foundation of study which can be expanded in later years.

Dr. Tori, who is in charge of teaching nuclear physics applied to medicine at the University of Bologna, has attempted this task and has succeeded very well. This book is tailor-made for the training of residents and gives them all the essential facts with a clarity of expression and a completeness of presentation seldom found in teaching manuals.

Dr. Tori begins with the fundamental concepts of matter and energy and with the interaction of energy and matter. This is followed by a discussion of measurements of quantity and quality of radiation. The various types of radiation generators and the natural and artificial radioactivity and its measurement are described.

The second section of the book is devoted to radiobiology, and includes the general effects of radiation on cells and, specifically, the effects of radiation on each tissue. The discussion on the direct effect of radiation on the gonads is amplified by a description of genetic effects. The effects of radiation on pathologic tissues are described in detail.

The third section of the book deals with dosimetry as applied to fixed and mobile beams of radiation, with filters and with grids, and it considers the spatial and chronologic distribution of radiation effects, treatment planning, contraindications, association of radiation therapy with surgery, general and local reaction and prognosis in specific cases.

The fourth section deals with the radiation therapy of various disease entities, beginning with cancer of the lip and ending with functional therapy of hypertension, Raynaud's disease and asthma. It gives detailed instruction on how to conduct treatments and it covers the whole field of the application of radiation therapy. This section is generally excellent, but the emphasis placed on radiation therapy of nonmalignant diseases may be considered excessive by some American radiologists.

An appendix deals with protection of personnel and patients from radiations produced by various agents and at various levels of energy.

This is an excellent book, concise and to the point, and is especially adapted for the instruction of residents. Since Dr. Tori speaks English fluently, it is to be hoped that he will translate this book into the English language for the benefit of English and American residents.

Cesare Gianturco, M.D.

Genetics and Cancer; A Collection of Papers Presented at the Thirteenth Annual Symposium on Fundamental Cancer Research, 1959. Edited by the Staff of The University of Texas M. D. Anderson Hospital and Tumor Institute. Cloth. Price, $8.50. Pp. 459, with numerous illustrations. The University of Texas Press, Austin 12, Texas, 1960.

This volume consists of twenty-two articles by eminent scientists from England, France, Sweden and the United States, an introduction by R. Lee Clark, Jr., Director and Surgeon-in-Chief, the University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas, and a summary by Howard B. Andervont, National Cancer Institute, Bethesda, Maryland. Together, they constitute a thorough and authoritative review of the topics considered.

The material is divided into six sections. The first, *Genetic Theory of Cancer Etiology*, includes three papers on plasmagenes, somatic mutations and lysogens. Six papers are devoted to the next subject, *Fundamental Aspects of Genetics in Carcinogenesis*, and five to the section on *Gene Interaction in Neoplastic Growth.* The

Bertner Foundation Lecture was part of this symposium and is entitled, "The Role of Virus and Host in Determining the Host Reaction to the Fibroma-Myxoma Virus Complex." Three papers deal with the *Genetic Basis of Cell Resistance*, and the four papers on *Heredity and Human Cancer* point out the progress and methods of study in human genetics, and the genetic consideration in human cancer.

It should be added that this volume brings together many concepts on the all important question of genetics and cancer. Conversely, because of the ever increasing fundamental knowledge in this field, many modifications and changes in these concepts may be anticipated in the near future.

Johanna Blumel, Ph.D.

Radiologische Exploration des Bronchus. By Dr. S. Di Rienzo, Professor für Radiologie an den Universitätskliniken Cordoba; and Dr. H. H. Weber, Facharzt für Radiologie, Bern. Cloth. Price, $12.85. Pp. 281, with 268 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart, Germany, 1960. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

The construction of the walls of the bronchi and bronchioles makes it possible for them to have physiologic motion and thus to dilate and to constrict. The embryology, histology, and anatomy of the bronchial system are described briefly. There are good illustrations of the bronchopulmonary segments.

Dr. Di Rienzo is well known for his technique in bronchography using serial roentgenography under fluoroscopic control. He aims to get the early, intermediate, and late phases of filling of the bronchi in each case. He claims that "alveolar" filling is possible only with the use of low viscosity contrast material. The significance of respiration and coughing regarding the size of the bronchial lumen and visualization of pathologic processes is very well demonstrated.

The value of bronchography in cases of congenital anomalies of the bronchi, asthma and emphysema and, of course, in bronchiectasis is discussed *in extenso*. In asthma there are, among other findings, a narrowing of all the bronchi of the second, third, and fourth order, a slow progression of the contrast material, considerable stasis in the small bronchi, and failure of filling of the acini. The appearance of the bronchial tree in Echinococcus of the lung is discussed in great detail with numerous beautiful illustrations of some of the authors' cases.

Bronchography is especially valuable in the early diagnosis of bronchogenic carcinoma in that it enables one to study the physiologic and pathologic dynamics of the normal and abnormal bronchi. The exact location and number of lung abscesses can be discovered with bronchographic study; similarly, with empyema. This method of study is also valuable in observing the postoperative bronchial stump.

Samuel Richman, M.D.

Medical X-Ray Technique; Principles and Applications. By G. J. van der Plaats, Chief Radiologist of the X-Ray Department at St. Annadal Hospital, Maastricht, and former Professor of Radiology in the University of Groningen. Cloth. Price, $10.00. Pp. 480, with 213 illustrations. The Macmillan Company, 50 Fifth Avenue, New York 11, N. Y., 1959.

This work gives a thorough, at times quite technical, description of the operation and construction of most roentgen-ray equipment and accessories in use today. It is written for the technician and provides him with a broad, detailed understanding of these tools. The author presupposes a knowledge of basic physical concepts, but he includes a chapter on radiation physics which is quite comprehensive. Throughout the book, the tone is scientific and it stresses the physical foundation of this medical field, since the author's concern here is not with teaching the standard roentgenographic techniques and positions.

The book is recommended to those technicians who desire a more detailed knowledge of the equipment they use daily in diagnosis and therapy. Radiologists may want to add this volume to their libraries for the same reason.

David Morse, Jr., M.D.

Pneumostratigrafia Cerebrale Normale. By M. Lenzi, G. C. Canossi, and G. Bassani. Price, L. 3,000. Pp. 92, with 57 illustrations. Minerva Medica, Società Tipografica Editrice, Bologna, Italy, 1959.

For several years, Professor Lenzi and his coworkers have applied laminagraphy to differentiate the superimposed and confusing shadows usually seen at encephalography.

This work is essentially an atlas in which normal laminagrams made at encephalographic

examination, taken serially at various levels, are shown and interpreted by schematic drawings with labelled structures. This approach is very satisfactory. The legends are printed both in Italian and in English, making this book useful for readers of the English language.

The atlas proper is preceded by a short text explaining the principles involved and the techniques employed. In this text the authors describe their method of fractionated gas filling and the special laminagraphic apparatus which they have developed for this type of work.

C. Gianturco, M.D.

Röntgenanatomie. By Prof. Dr. med. D. Nagy, Vorstand des Institutes für chirurgische Anatomie und experimentelle Chirurgie der medizinischen Universität, Budapest. Cloth. Pp. 509, with 545 illustrations. Akadémiai Kiadó, Budapest, 1959.

This book on roentgen anatomy exemplifies the attention to detail and thoroughness of coverage usually given to a subject by most Continental writers. The author illustrates each anatomic region by means of photographs to show the positions utilized for each examination. Photographs and drawings depict the relationships between surface landmarks and underlying structures. Anatomic dissections in clear detail further aid in revealing structural relationships.

The book is profusely illustrated with negative image roentgenograms which are more familiar to us than the positive image reproductions often found in foreign texts. They are of the highest quality throughout the book.

Of particular value is the chapter dealing with the anatomy of the pulmonary segments, bronchi and vessels; it is well illustrated with bronchograms and laminagrams. Photographs of the dried skull in various projections supplemented by roentgenograms of these specimens and the living subject are effectively used in another outstanding chapter.

This book is an excellent German text on the subject of roentgen anatomy and an especially fine example of quality in the reproduction of medical material.

David Morse, Jr., M.D.

BOOKS RECEIVED

Strahlenschutz in Klinik und Ärztlicher Praxis. By Prof. Dr. med. Werner Lorenz, Oberarzt am Röntgen- und Strahleninstitut der Johannes Gutenberg, Universität Mainz. Cloth. Price, $15.70. Pp. 259, with 62 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart, Germany, 1961. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

Technik der Röntgendiagnostik. By Priv.-Doz. Dr. Hanno Poppe, Leiter des Röntgeninstituts der Chirurg. Univ.-Klinik Göttingen, Oberarzt der Klinik; Ilse Lohstöter, 1. Med.-techn. Assistentin des Röntgeninstituts der Chirurg. Univ.-Klinik Göttingen; and Dr. Ph. Lauwers, Direktor der Abt. für Röntgen und wissenschaftliche Anwendungen Gevaert Photo-Producten N. V. Mortsel (Antwerpen), Belgium. Cloth. Price, $20.95. Pp. 623, with 328 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart, Germany, 1961. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

Annual Review of Nuclear Science. Volume 10. Edited by Emilio Segrè, University of California; Gerhart Friedlander, Brookhaven National Laboratory; and Walter E. Meyerhof, Stanford University. Cloth. Price, $7.00. Pp. 617. Annual Reviews, Inc., 231 Grant Ave., Palo Alto, Calif., 1960.

The Year Book of Radiology (1960–1961 Year Book Series). Edited by John Floyd Holt, M.D., Professor, Department of Radiology, University of Michigan; Walter M. Whitehouse, M.D., Associate Professor, Department of Radiology, University of Michigan; Harold W. Jacox, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Morton M. Kligerman, M.D., Professor of Radiology and Chairman of the Department of Radiology, Yale University School of Medicine, Director of Radiology, Grace-New Haven Community Hospital. Cloth. Price, $11.00. Pp. 441, with 305 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago, Ill., 1960.

Congenital Malformations of the Heart; Volume I: General Considerations. Second edition. By Helen B. Taussig, M.D., Professor of Pediatrics, Johns Hopkins University School of Medicine; Physician-in-Charge, Cardiac Clinic, Harriet Lane Home, Johns Hopkins Hospital. Cloth. Price, $4.75. Pp. 204, with numerous illustrations. Published for The Commonwealth Fund by Harvard University Press, Cambridge 38, Mass., 1960.

Comparative Anatomy, Pathology and Roentgenology of the Breast. By Helen Ingleby, M.D., M.R.C.P., Late Professor of Pathology, Woman's Medical College of Pennsylvania; Research Pathologist on Diseases of the Breast, Albert Einstein Medical Center, Philadelphia, Pennsylvania; and Jacob Gershon-Cohen, M.D., D.Sc. (Med.), Department of Radiology, Albert Einstein Medical Center; Assistant Professor of

Radiology, Graduate School of Medicine, University of Pennsylvania. Cloth. Pp. 472 with 201 illustrations. University of Pennsylvania Press, 3436 Walnut St., Philadelphia 4, Pa., 1960.

La Lumière Bleue; Luminescence par effet de sillage dans les milieux transparents soumis aux radiations de haute énergie. By Lucien Mallet. Paper. Pp. 150, with 53 illustrations. J.-B. Ballière & Fils, Editeurs, 19, Rue Hautefeuille, Paris 6^e, France, 1960.

Abridged Scientific Publications from the Kodak Research Laboratories. Volume XXXIV. Paper. Pp. 253. Eastman Kodak Company, Rochester, N. Y., 1960.

Transcript of the Workshop on Bone Densitometry; held at the Stone House, National Institutes of Health, Bethesda, Maryland, December 4, 5, 1959. Paper. Pp. 240. Fels Research Institute for the Study of Human Development, Yellow Springs, Ohio, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 11—Supplementum 44; Cardiopulmonary Hemodynamics in Chronic Lung Disease with Special Reference to Pulmonary Tuberculosis. By Carsten Müller. Paper. Pp. 369. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1959.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 45; Influence of Anions and Cations with a Long Hydrocarbon Chain on the Thrombin-Fibrinogen Reaction. By Kristoffer Korsan-Bengtsen. Paper. Pp. 86. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 46; Haemophilia; A Study of Its Laboratory, Clinical, Genetic and Social Aspects Based on Known Haemophiliacs in Finland. By Eero Ikkala. Paper. Pp. 144. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 47; Studies on Urinary Excretion of δ-Aminolaevulic Acid and Other Haem Precursors in Lead Workers and Lead-Intoxicated Rabbits. By Birgitta Haeger-Aronsen. Paper. Pp. 128. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 48; Methodische und Klinische Untersuchungen über die Ausscheidung der 3-Methoxy-4-Hydroxymandelsäure im Urin. By Wilfried von Studnitz. Paper. Pp. 73. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 49; The Direct Diazo Reaction of Bile Pigments in Serum; Experimental and Clinical Studies. By Bertil Nosslin. Paper. Pp. 176. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Deauville Hotel, Miami Beach, Fla., Sept. 26–29, 1961.

American Radium Society
Secretary, Dr. Charles G. Stetson, 350 Engle Street, Englewood, N. J. Annual meeting: Broadmoor Hotel, Colorado Springs, Colo., May 10–14, 1961.

Radiological Society of North America
Secretary, Maurice Doyle Frazer, 1037 Stuart Bldg., Lincoln, Neb.
Treasurer, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual Meeting: Palmer House, Chicago, Ill., Nov. 26–Dec. 1, 1961.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting to be announced.

Section on Radiology, American Medical Association
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: New York City, June 26–30, 1961.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building. Rochester, Minn. The Spring 1961 examination will be held at the Denver Hilton Hotel, Denver, Colorado, June 19–22, inclusive; the deadline for filing applications was January 1, 1961. There will be no Special Examination in Nuclear Medicine. The Fall 1961 examination will be held at the Shoreham Hotel, Washington, D. C., December 4–7, inclusive; the deadline for filing applications is July 1, 1961. A Special Examination in Nuclear Medicine will be offered if there are sufficient applications.

Tenth International Congress of Radiology
Secretary-General, Dr. Carleton B. Peirce, Royal Victoria Hospital, Montreal 2, Quebec, Canada. Meets in Montreal, Aug. 26–Sept. 1, 1962.

Seventh Inter-American Congress of Radiology
Counselor for the United States, Dr. J. A. del Regato, Penrose Cancer Hospital, 2200 North Cascade Avenue, Colorado Springs, Colorado. The meeting will be held in São Paulo, Brazil, September 3–10, 1961.
Secretary-General, Dr. Walter Bomfim-Pontes, Rua Cesario Motta, No. 112, São Paulo.

Alabama Radiological Society
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

American Nuclear Society
Executive-Secretary, Octave J. Du Temple, 86 E. Randolph St., Chicago, Ill.

Arizona Radiological Society
Secretary, Dr. Don E. Matthieson, 926 East McDowell Rd., Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. J. B. Scruggs, Arkansas Baptist Hospital, Little Rock, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary, Dr. Melvin M. Figley, Department of Radiology, University of Washington, Seattle 5, Wash. Annual meeting to be announced.

Atlanta Radiological Society
Secretary, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

Blockley Radiological Society
Secretary, Dr. Samuel Finkelman, 101 S. Twentieth St. Philadelphia, Pa.

Brooklyn Radiological Society
Secretary, Dr. Joseph Arcomano, 168 Clinton St., Brooklyn 1, N. Y. Meets first Thursday of each month October through May.

Buffalo Radiological Society
Secretary, Dr. Kenneth H. Seagrave, 537 Delaware Ave., Buffalo 2, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Radiological Society
Secretary, Dr. Joseph A. Head, 150 Marshall St., Syracuse, N. Y. Meets first Monday each month October through May.

Central Ohio Radiological Society
Secretary, Dr. Robert L. Freidman, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary, Dr. William F. Hutson, 5145 N. California Ave., Chicago, Ill. Meets second Thursday of each month, October to April except December at the Sheraton Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary, Dr. Norman E. Berman, 14404 S. Park Blvd., Shaker Hgts. 20, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

Colorado Radiological Society
Secretary, Dr. Bertram L. Pear, 3705 East Colfax Ave., Denver 6, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. James L. Krieger, 85 Jefferson St., Hartford, Conn. Meets first Friday in February and April.

Dallas-Fort Worth Radiological Society
Secretary, Dr. F. J. Bonte, 5201 Harry Hines Blvd., Dallas 35, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit 1, Mich. Meets monthly first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

East Tennessee Radiological Society
Secretary, Dr. J. Marsh Frere, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.

Eastern Conference of Radiology
Secretary, Arrangements Committee, Dr. Philip Myers, Baltimore City Hospital, Baltimore 24, Md. Annual meeting: Lord Baltimore Hotel, Baltimore, Md., March 9–11, 1961.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Eastern Radiological Society
Secretary, Dr. John D. Osmond, Jr., Euclid-Glenville Hospital, Cleveland 19, Ohio. Meets at Mid Pines Club Southern Pines, N. C., April 16–19, 1961.

Florida Radiological Society
Secretary, Dr. Alfred G. Levin, 837 DuPont Bldg., Miami, Fla. Meets twice annually, in the spring with the annual State Society Meeting, and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.

Georgia Radiological Society
Secretary, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Miami Radiological Society
Secretary, Dr. Donald H. Altman, 2751 Coral Way, Miami, Fla. Meets monthly third Wednesday at 8 P.M. at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Radiological Society
Secretary, Dr. Harvey A. Humphrey, 462 N. Taylor, St. Louis 8, Mo.

Houston Radiological Society
Secretary, Dr. John Douglas Reeve, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.

Idaho State Radiological Society
Secretary, Dr. Claude W. Barrick, St. Alphonsus Hospital, Boise, Idaho. Meets in the Spring and Fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. David E. Wheeler, 1500 North Ritter, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary, Dr. Lewis G. Allen, 807 Huron Bldg., Kansas City, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. Robert H. Akers, V. A. Hospital, Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Walter Stilson, 1720 Brooklyn Ave., Los Angeles, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. Albert A. Poulin, Thayer Hospital, Waterville, Maine. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

Memphis Roentgen Society
Secretary, Dr. Hollis H. Halford, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. S. F. Johnson, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. Joseph F. Wepfer, 5000 W. Chambers St., Milwaukee 10, Wis. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.

Mississippi Radiological Society
Secretary, Dr. Jack K. Goodrich, University Medical Center, Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
Secretary, Dr. J. K. Boughn, 35 11th Ave., Helena, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Alan E. Baum, 100 Nowbridge Rd., Hicksville, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. Ronald E. Waggener, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Nebraska. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through May at The Longwood Towers, Brookline, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Albert A. Dunn, 622 W. 168th St., New York, N. Y. Meets monthly on third Monday, New York Academy of Medicine at 4:30 P.M.

North Carolina Radiological Society
Secretary, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. R. F. Raasch, Post Office Box 990, Dickinson, North Dakota. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Lester I. Citrin, St. Mary's Hospital, Troy, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. Paul D. Meyer, 125 S. Grant Ave., Columbus, Ohio. Annual meeting third week end in May, 1961 at Columbus, Ohio.

Oklahoma State Radiological Society
Secretary, Dr. E. D Greenberger, Medical Arts Bldg., McAlester, Okla. Meets in January, May and October.

Oregon Radiological Society
Secretary, Dr. George R. Satterwhite, 1123 S.W. Yamhill, Portland, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Portland, Oregon, May, 1961.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Frederick R. Gilmore, 234 State St., Harrisburg, Pa. Annual meeting: Bedford Springs Hotel, May 26–27, 1961.

Philadelphia Roentgen Ray Society
Secretary, Dr. Robert B. Funch, Department of Radiology, Germantown Hospital, Philadelphia 44, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Ross H. Smith, St. Margaret Memorial Hospital, Forty-Sixth St., Pittsburgh 1, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

Radiological Section, Baltimore Medical Society
Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Society of Greater Cincinnati
Secretary, Dr. Donald Janny, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. Philip S. Arthur, 274 Young Hotel Bldg., Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Robyn Hardy, 4324 Magnolia St., New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. Austin J. Tidaback, 912 Prospect Ave., Plainfield, N. J. Meets at Atlantic City at time of State Medical Society meeting and in November in Newark, N. J.

Radiological Society of New York State
Secretary-Treasurer, Dr. Mario C. Gian, 610 Niagara St., Buffalo 1, N. Y. Annual meeting to be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary, Dr. Joseph F. Linsman, 436 N. Roxbury Dr., Beverly Hills, Calif.

Redwood Empire Radiological Society
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Robert H. Greenlaw, 188 Irvington Rd., Rochester 20, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: Denver Hilton Hotel, Denver, Colo., Aug. 10–12, 1961.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
Secretary, Dr. Stanley A. Moore, 2466 First Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. M. A. Sisson, 450 Sutter St., San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bimonthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. William E. Sheely, 1746 K St., N.W., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

Section on Radiology, Southern Medical Association.
Secretary. Dr. Seymour Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La. Annual meeting to be announced.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary, Dr. Richard G. Lester, 412 Union St., S.E., Minneapolis 14, Minn. Annual meeting: Deaville Hotel, Miami Beach, Fla., Sept. 25, 1961.

Society of Nuclear Medicine
Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. *Administrator*, Samuel N. Turiel, 4[illegible]0 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Penn Sheraton Hotel, Pittsburgh, Pa., June 14–17, 1961.

South Bay Radiological Society
Secretary, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

Southern Radiological Conference
Secretary, Dr. Marshall Eskridge, Mobile Infirmary Mobile, Ala.

Southwestern Radiological Society
Secretary, Dr. Ralph S. Clayton, 1501 Arizona, Bldg. 2-A, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
Secretary, Dr. James J. Range, P.O. Box 324, Johnson City, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1[illegible]16 Pennsylvania Ave., Fort Worth 4, Texas. Next meeting January 20 and 21, 1961, Texas Hotel, Fort Worth, Texas.

TRI-STATE RADIOLOGICAL SOCIETY
Secretary, Dr. James R. Mathews, 118 S. E. First St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

UPPER PENINSULA RADIOLOGICAL SOCIETY
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. Powell G. Dillard, Jr., 715 Church Street, Lynchburg, Va. Meets annually in October.

WASHINGTON STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph T. Houk, 14303 Ambaum Blvd., Seattle 66, Wash. Meets third Monday of each month from September through April at the University of Washington Medical School.

WEST VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. Karl J. Myers, 112 N. Woods St., Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

WESTCHESTER RADIOLOGICAL SOCIETY
Secretary, Dr. Richard P. Avondu, Yonkers General Hospital, Park & Ashburton Ave., Yonkers, N. Y. Meets on third Tuesday of January and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY
Secretary, Dr. Howard G. Bayley, 116 Iroquois Parkway, Beaver Dam, Wis. Annual meeting each spring in various places.

X-RAY STUDY CLUB OF SAN FRANCISCO
Secretary, Dr. John H. Heald, 450 Sutter St., San Francisco 8, Calif. Meets monthly, third Thursday at 7:30 P.M., Children's Hospital, September through June.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

ASOCIACIÓN DE RADIÓLOGOS DE CENTRO AMERICA Y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Julio Toriello, 11 Calle 2-37, Zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

SOCIEDAD DE RADIOLOGÍA DE EL SALVADOR
Secretary, Dr. Rafael Vega Gómez.

SOCIEDAD DE RADIOLOGÍA DE GUATEMALA
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPÍA CUBANA
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

SOCIEDAD COSTARRICENSE DE RADIOLOGIA
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

SOCIEDAD MEXICANA DE RADIOLOGÍA, A. C.
Calle del Oro No. 15, México 7, D. F.
Secretary-General, Dr. E. Alvarez Hernández. Meets first Monday of each month.

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

SOCIEDAD RADIOLÓGICA PANAMEÑA
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

SOCIEDAD RADIOLÓGICA DE PUERTO RICO
Secretary, Dr. César E. Rosa-Perez, Fondo del Seguro del Estado, Parada 1, San Juan 8, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

ASSOCIATION OF RADIOLOGISTS OF THE PROVINCE OF QUEBEC
Secretary, Dr. Odilon Raymond, 5400 Blvd. Gouin. Quest, Montreal, Que. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY INCORPORATED WITH THE RÖNTGEN SOCIETY
Honorary Secretary, Dr. John Blewett, 32 Welbeck St., London, W. 1. Meets monthly from October until May.

FACULTY OF RADIOLOGISTS
Honorary Secretary, Dr. R. A. Kemp Harper, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting to be announced.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDICINE ((CONFINED TO MEDICAL MEMBERS),
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1.

CANADIAN ASSOCIATION OF RADIOLOGISTS
Honorary Secretary, Dr. Robert G. Fraser, *Associate Honorary Secretary*, Dr. Jean-Louis Léger, 1555 Summerhill Ave., Montreal 25, Que. Annual meeting to be announced.

MONTREAL RADIOLOGICAL STUDY CLUB
Secretary, Dr. F. McConnell, 1650 Cedar Ave., Montreal, Quebec. Meets first Tuesday evening, October to April.

SECTION OF RADIOLOGY, CANADIAN MEDICAL ASSOCIATION
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTRO-RADIOLOGIE MÉDICALE
General Secretary, Dr. Louis Ivan Vallée, 1058 rue St-Denis, Montreal 18, Canada. Meets third Saturday each month.

TORONTO RADIOLOGICAL SOCIETY
Secretary, Dr. L. R. Harnick, Toronto Western Hospital, 399 Bathurst St., Toronto, Ontario. Meets second Monday of each month September through May.

COLLEGE OF RADIOLOGISTS OF AUSTRALASIA
Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

SOUTH AMERICA

ASOCIACIÓN ARGENTINA DE RADIOLOGÍA
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

ATENEO DE RADIOLOGIA
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.

COLÉGIO BRASILEIRO DE RADIOLOGIA
Secretary-General, D. Camillo Segreto, Avenida Angélica, 1.170, Caixa Postal 5984, São, Paulo, Brazil.

SOCIEDAD ARGENTINA DE RADIOLOGÍA, JUNTA CENTRAL BUENOS AIRES
Secretary, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.

SOCIEDAD BOLIVANA DE RADIOLOGÍA
Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

SOCIEDADE BRASILEIRA DE RADIOLOGIA
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

SOCIEDADE BRASILEIRA DE RADIOTERAPIA
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

SOCIEDAD CHILENA DE RADIOLOGÍA
Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25–31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Perú. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris.
Secretary-General, Dr. Ch. Proux, 9, rue Daru, Paris 8^e, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut. Lagenbeckstr. 1, Mainz, Germany. Annual meeting: April 16–19, 1961, in Hamburg.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Electrologie en Röntgenologie
Secretary, Dr. J. R. von Ronnen, Violenweg 14, den Haag Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The next list of Meetings of Radiological Societies will be published in the May, 1961 issue of the Journal.

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

HEAD

FEINBERG, S. B. Congenital mesodermal dysmorpho-dystrophy (brachymorphic type). *Radiology*, Feb., 1960, *74*, 218–224. (Address: 737 E. 22nd St., Minneapolis 4, Minn.)

Dysmorpho-dystrophia mesodermalis congenita, or congenital mesodermal dystrophy, appears to be a suitable broad category in which to include the findings described by Marfan at one extreme (*i.e.*, the hypoplastic, arachnodactylic, or dolichomorphic type) and Marchesani at the other (*i.e.*, the hyperplastic, brachydactylic, or brachymorphic type). Marchesani's syndrome *per se* has not been reported in either the American or foreign radiologic literature, although it has been described in the publications in other fields. The syndrome includes short stature, a brachycephalic skull, brachydactyly, well-developed subcutaneous tissues, myopia and glaucoma with frequent association of spherical and/or dislocated lenses, and sometimes congenital heart defects. A familial tendency and consanguinity in the parents have been reported.

Roentgenologically, the skull, facial bones, hands, and feet have been the primary areas of involvement. The most obvious finding is grotesque exaggeration of brachycephaly, with small, shallow, closely placed orbits, diminutive maxillae, hypoplastic zygomatic arches, arched palate, and either actually or relatively prognathic mandible. The presence of depressed maxilla and prognathic mandible set this syndrome apart from craniofacial mandibular dysostosis.

Two cases are presented, occurring in sisters aged ten and seven at the time of admission, with similar findings in each child. There was a history of retarded development, repeated respiratory infections, poor vision associated with headaches, fatigability, and recurrent ulcerations of the feet. Heart murmurs were discovered in each child in infancy. Each was noted to have a prominent forehead with abundant coarse hair extending low on the forehead and neck, hypoplastic maxillae with a high arched palate and maldeveloped, deformed, and misdirected teeth. The mandible appeared prognathic. There were small sunken eyes with lids which could not completely open and reversed lid angles. There was poor vision associated with abnormalities of the ocular structures. The hands and feet were short and broad, as well as thick. The skin folds, especially about the hands and thighs, were thickened, and the hands showed ulnar deviation. There was clinical and roentgenologic evidence of patent ductus arteriosus, which was corrected surgically in each child. Roentgenographic findings included the strikingly brachycephalic skull, with shallow, hypoplastic, asymmetric orbits, hypoplastic and depressed maxillae, maldeveloped teeth, and relatively prognathic mandible. The metacarpals, metatarsals, and phalanges were short and broad, and one child had roentgen evidence of retarded bone age. The long bones were somewhat short but not broad.—*Walter H. Jarvis, Jr., M.D.*

GENITOURINARY SYSTEM

HILDRETH, EUGENE A., PENDERGRASS, HENRY P., TONDREAU, RODERICK L., and RITCHIE, DAVID J. Reactions associated with intravenous urography: discussion of mechanisms and therapy. *Radiology*, Feb., 1960, *74*, 246–254. (Address: E. A. Hildreth, Hospital of the University of Pennsylvania, Philadelphia 4, Pa.)

The use of iodide compounds for intravenous urography is increasing rapidly. In the United States alone there has been a fivefold increase in the past fourteen years and, as a result, more fatal as well as nonfatal reactions are being reported each year. The clinical picture of reactions associated with intravenous urography is that of a mild toxic reaction or an allergic reaction. The mild toxic reactions consist of phlebitis, pain in the arms, nausea, flushing, giddiness, tingling, numbness, and cough. These seldom proceed to more serious consequences. The allergic reactions may be mild (urticaria, conjunctivitis or rhinitis) or severe (dyspnea, shock, or cyanosis). These allergic reactions are the ones that endanger life.

The exact mechanism of the reactions to organic contrast media is not clear but at least three possible causes have been considered: toxicity, pharmacologic idiosyncrasy, and allergy. Neither pharmacologic idiosyncrasy nor toxicity can be implicated seriously. The exceptions, where toxicity was a major factor, have been observed chiefly in children receiving large doses and in patients otherwise seriously ill. The available evidence indicates that allergy is the chief cause of serious and fatal reactions.

At present reactions to the iodides cannot be predicted accurately. A history of allergy can be used as a warning but is not of itself an absolute contraindication. Also, as the authors state, "the immediate wheal and erythema skin tests (reagenic type) are worthless in predicting reactions to the iodides now being used in contrast study." Therefore, it is suggested that the most practical approach is to test the patient by observing his tolerance for a small dose of the medium. An experimental program is presented that may be of value or may lead to new techniques in preventing reactions. This consists of a careful history, prior subcutaneous testing with dilute contrast material, a small test dose at the time of examination, and careful observation for reactions following the injection.

When reactions occur they can immediately assume the most serious proportions. Therefore, the

first step in therapy is the establishment of an emergency plan of action. If allergic manifestations appear, therapy proceeds according to the type of reaction. The reactions of dyspnea wheezing or cyanosis are immediately treated with epinephrine (intramuscularly administered epinephrine HCl, 1:1000, 0.5 cc.) with concurrent attention to proper oxygenation and establishment of an airway if cyanosis appears. If shock appears, longer acting vasopressors are used. It is emphasized that convulsions are most often associated with cyanosis and are due to anoxia. Barbiturates are helpful in convulsions not due to anoxia but they would be harmful in the presence of cyanosis.

For the reactions of asthma and pulmonary edema, epinephrine is recommended although aminophylline and prednisolone 21-phosphate are valuable. In the event of total vascular collapse and coma, the authors recommend epinephrine, the shock position, vasopressors, oxygen and prednisolone 21-phosphate. Laryngeal edema is rare but is best treated with epinephrine with or without tracheotomy. Cortisone-like drugs are not useful in the first critical minutes and respiratory stimulants and calcium therapy have no value. In the event of cardiac arrest, the authors suggest the simpler methods of cardiac resuscitation such as blows to the chest, cardiac stimulation by injections, and rocking the patients knees against his chest.—*Edward B. Best, M.D.*

Skeletal System

McGavran, M. H., and Spady, H. A. Eosinophilic granuloma of bone; a study of twenty-eight cases. *J. Bone & Joint Surg.*, Sept., 1960, *42-A*, 979–992. (From: Division of Surgical Pathology and Orthopaedic Surgery, Department of Surgery, Washington University School of Medicine, Barnes Hospital, St. Louis Children's Hospital, and the Barnard Free Skin and Cancer Hospital, St. Louis, Mo.)

This is a review of 28 proved cases of eosinophilic granuloma of bone. All but 1 were symptomatically single. Clinical observations must be considered in arriving at a diagnosis and patients with dermatitis, lymphadenopathy, hepatosplenomegaly, anemia, thrombopenia, otitis media, diarrhea, diabetes insipidus or pulmonic infiltration were classified as either Abt-Letterer-Siwe disease or Hand-Schüller-Christian syndrome.

There were 15 male and 13 female patients with an average age of 13.3 years. Only one patient was over 30. The common sites of the lesions were the skull and femur, each with 7 lesions and the ribs and mandible with 3. Pain of short duration was the presenting symptom. The laboratory studies were not of diagnostic assistance. In 1 case out of 9 in which bacterial cultures were done, the authors isolated an atypical acid fast organism on culture but were unable to determine its significance.

Roentgenologically, the lesions in the flat bones appeared as sharply defined, "punched-out" areas. None had button sequestra. A dermoid cyst may have a similar appearance. The rib lesions were lobulated, destructive and expansile with slight periosteal reaction. In the long bones there was no involvement of the epiphyses. In children the lesions may be difficult to differentiate from Ewing's tumor or osteomyelitis, since they are a destructive process with erosion of the cortex and moderate to marked new bone formation with periosteal layering. In adults the lesions in the long bones showed as ill defined central radiolucencies with little cortical erosion or periosteal reaction.

No plan of therapy was followed routinely. The skull and rib lesions were usually excised. The other lesions were not treated or had curettage or irradiation.

Serial roentgenograms were available in only 9 cases, but in all 28 no signs or symptoms persisted after treatment. In 1 case a soft tissue implant developed in the scar after biopsy and irradiation. There were no cases with transition to Hand-Schüller-Christian disease.

The authors urge careful microbiologic study of the tissues removed at surgery to better clarify the etiology of these lesions.—*Martha Mottram, M.D.*

Aakhus, Trygve, Oddvan, Eide, and Stokke, Trovald. Parosteal osteogenic sarcoma. *Acta radiol.*, July, 1960, *54*, 29–40. (From: The General Department and the Pathology Laboratory, The Norwegian Radium Hospital, Oslo, Norway.)

The authors present their experiences with 5 cases of parosteal osteogenic sarcoma selected from their 85 cases of osteogenic sarcoma over a fifteen year period, and briefly review the literature. Their findings were essentially the same as reported previously.

Thirty-four previous cases have been reported. There is no sex predominance. The average age is higher than in cases of osteogenic sarcoma with 44 per cent being over thirty years of age. Duration of symptoms is prolonged. The tumor is usually metaphyseal with the distal femur being the most common location.

The roentgenologic appearance is described as a juxtacortical, broad-based, densely ossified mass. Sclerosis is most marked at the base with an irregular periphery. Rarefactions may be present within the tumor. Characteristically, the tumor encircles the shaft with cortical thickening at the point of attachment. The usual signs of malignancy are absent. The appearance may remain unchanged for years. Recurrence after inadequate excision may appear in the surrounding soft tissues.

The histologic appearance of the tumor is characteristic in typical cases. However, findings will vary from one area of the lesion to another, often causing under-rating of the tumor by the pathologists.

Of the 39 patients, 8 died after an average of eight years. One of these was treated by irradiation; the others by surgery. Twenty-one are alive after an average of seven years. Sixteen had primary excisions; the others amputations. Ten died of other causes, or the information obtained was unreliable. The authors feel that radiation therapy is of little avail. Permanent cure can be expected only after wide excision. Recurrence is common after local excision with the recurrent tumor being more highly malignant. Ultimately, extensive metastases are found. These often are slow growing.

Similar lesions are briefly discussed. Myositis ossificans and ossifying subperiosteal hematomas usually have a preceding history of trauma. These also tend to reach a maximum size and then regress. An osteochondroma usually does not encircle the shaft and has a core of cancellous tissue continuous with the medulla. Sclerotic osteogenic sarcoma is rapidly growing, has the characteristics of malignancy, and is usually associated with systemic reactions.—*Barry Gerald, M.D.*

Aitken, A. P., and Nalebuff, E. A. Volar transnavicular perilunar dislocation of the carpus. *J. Bone & Joint Surg.*, Sept., 1960, *42-A*, 1051–1057. (From: Orthopaedic Service, Boston City Hospital, Boston, Mass.)

The usual perilunar dislocation is of the dorsal type with a transnavicular fracture.

A case is presented of a twenty-one year old male who fell and landed on the dorsum of the flexed hand, sustaining a volar perilunar dislocation with fracture of the navicular. The larger distal navicular fragment was displaced anteriorly while the other carpal bones and the smaller proximal fragment remained with the lunate. Reduction was easily obtained with traction. The position could be maintained in moderate extension. The hand was immobilized for ten weeks. The navicular showed non-union. There was aseptic necrosis of the lunate at fourteen months, but at two and one-half years this had revascularized.

In falls on the extended hand either an anterior dislocation of the lunate or a retrolunar dislocation of the other carpal bones may be produced, depending on the degree of extension and direction of force. In falls on the flexed hand, there may be an extremely rare dorsal dislocation of the lunate or a volar perilunar dislocation of the carpal bones. These latter lesions are uncommon due to the natural tendency to extend the hand in a fall.

The prognosis in perilunar dislocation is guarded, particularly when associated with fracture of the navicular. Aseptic necrosis will occur in 50 per cent or more of the fractures.—*Martha Mottram, M.D.*

Packer, James M., Harris, Elmer J., and Henderson, Robert P. Bilateral synostosis of seventh rib and scapula; a case report. *Radiology*, Feb., 1960, *74*, 289–290. (Address: J. M. Packer, 1190 North State St., Jackson 2, Miss.)

The authors report a single case of bilateral, symmetric, congenital synostosis between the seventh posterior ribs and the inferior angles of the scapulae. This proved to be an isolated skeletal anomaly in a patient who had led an active life with no significant disability except for restriction of all motion of the shoulder and upper extremity involving scapular movement. This was the first time the authors had observed this type of anomaly and they were unable to discover in the literature published in the past ten years any article referring to this particular abnormality. There are many other commonly encountered types of rib abnormalities reported such as bifid anterior, hypoplastic and hyperplastic cervical ribs, and the group of synostoses and pseudoarthroses between adjoining ribs.—*W. M. McBride, M.D.*

Brou, M. (Luluabourg, Congo). Syndrome de Klippel-Feil chez un enfant Congolais. (The Klippel-Feil syndrome in a Congolese infant.) *J. belge de radiol.*, Mar., 1960, *43*, 221–226.

The authors report a case of a Klippel-Feil syndrome in a nine year old Congolese child, who was admitted with a diagnosis of Pott's disease. The child was of medium height with a moderately pronounced dorsolumbar kyphosis. There was a cervicodorsal scoliosis with convexity to the left in the lower half of the spine, with a reverse curvature in the upper half of the cervical spine and decreased mobility of the neck. Except for the obvious skeletal deformity, there were no abnormalities on physical examination. Laboratory tests were not contributory.

The distinguishing feature in the history was the fact that the deformity had not changed in appearance or degree since birth. This was considered, from a clinical point of view, as an argument against the diagnosis of Pott's disease.

The striking roentgen findings were fusion of the atlas and the axis, the butterfly appearance of C3 and C4 with dehiscence of the central portion of the bodies, congenital absence of C6 and C7, hemivertebra of D1 with agenesis of the left half and hemivertebra of D2 with agenesis of the right half, the butterfly appearance of D3 caused by incomplete fusion of the two lateral masses of the body, and a normal D4 with fusion of the bodies of the first four dorsal vertebrae but with adequate delineation of the

contour of each individual body being maintained. There were no abnormalities from D5 to D12. There was a cuneiform aspect of L1 and L2, as seen in the lateral projection, due to agenesis of the anterior halves with fusion of the bodies. There was no abnormality of the vertebrae below this point.

There was incomplete fusion of the first five right ribs. The right sixth rib was rather well defined but it was partially fused to the one immediately above. The two first left ribs were partially fused. The remaining ribs were not remarkable.

This is the first such case reported from the Congo and apparently is significant to the author because of the high incidence of Pott's disease in that area.—*William H. Shehadi, M.D.*

Blood and Lymph System

Puijlaert, C. B. A. J. Biphasic serial aorto-arteriography; (principles, method and apparatus). *J. belge de radiol.*, Mar., 1960, *43*, 261–274. (From: Radiological Department of St. Elizabeth Hospital, Tilburg, Holland.)

A method of adequately and simultaneously visualizing the circulation from the level of the distal aorta inferiorly to include both lower extremities is described. Angiograms are taken throughout the arterial and venous phases of the circulation. The necessity of visualizing such a large area lies in the fact that the location of pathology may be extensive and the rate of circulation in the two lower extremities may vary considerably depending upon the pathology present in one or the other.

The basis of this method is two injections made into the aorta through the same needle with an interval of approximately one minute. Manual exposures of the lower extremity are made after the first injection, followed by rapid semi-automatic exposures of the faster pelvic circulation after the second injection.

This method has a distinct advantage in that areas requiring different exposure times do not have to be visualized in one roentgenogram, thus avoiding needless exposure of either the extremities or the pelvis.

The simple apparatus consists essentially of a carrier for the two sets of films which is placed beneath the patient and is moveable in order to give some degree of overlapping.—*Everett G. Davis, Jr., M.D.*

Graumann, Walter. Methodik und Bedeutung der Splenoportographie. (Procedure and importance of splenoportography.) *Röntgen Blätter*, Sept., 1960, *13*, 257–271. (Address: Strahlenabteilung Augusta-Viktoria-Krankenhaus, Canovastr. 9, Berlin-Friedenau, Germany.)

Liver angiography can be performed in one of three ways: (1) by injecting contrast material directly into the hepatic artery, (2) by catheterizing three hepatic veins via the inferior vena cava (coincidental filling may occur during angiocardiography in tricuspid atresia), and (3) by injecting the medium into the spleen (splenoportography).

Whenever an injection into the spleen is performed, there is the small but definite risk of rupture of the splenic capsule, which could result in fatal hemorrhage. Therefore, splenic puncture should be done only in an institution in which facilities for immediate splenectomy are available. For the same reason it is preferable to puncture the spleen during general anesthesia with intubation; under bag-breathing, apnea may be induced for the roentgen exposures, and shallow respiratory movements during the time when the needle is actually in the spleen will minimize the risk of trauma to the splenic capsule.

It is farily simple to insert a needle into a large spleen but, when the spleen is of the usual size or smaller, it may be quite difficult to find the organ and to make the injection as close as possible to the splenic hilum so as to insure easy flow of the contrast material. The author prefers first to execute laparoscopy (peritoneoscopy) under general intubation anesthesia and, if he still needs more information, he will insert the needle into the spleen under endoscopic control.

After the needle has been placed, it is important to measure the pressure, which is done by attaching a U-shaped manometer. This necessitates keeping the needle in the spleen a few minutes longer than otherwise, but this measurement is sufficiently important to justify the additional, small risk. Then 30–55 cc. of contrast material is injected in 4–5 seconds. The entire procedure is performed with the patient on a roentgenographic table provided, if possible, with a seriograph.

The author uses a triphasic 1,000 ma.transformer and a tube-skin distance of 110 cm. with 88–92 kv. and 30–40 mas. (0.12–0.16 sec.). For the first ten seconds after the injection, one frame is exposed every second, then additional views are taken at 20, 30, and 40 seconds.

After termination of the procedure, the patient should rest for about four hours in the left lateral decubitus position. He should be kept under strict (preferably hospital) observation for seven days thereafter, because delayed hemorrhage is known to have occurred.

The actual puncture of the spleen is performed with a 12 cm. needle inserted through the ninth or tenth intercostal space, between the anterior and midaxillary line. If there is enlargement of the spleen, the puncture should be performed below the costal margin. When the spleen is smaller than normal, the patient may be placed in the prone position.

The value of splenoportography is to demonstrate the existence of portal hypertension, and to help the

surgeon decide which by-pass intervention has the better chance of success. The delay in portal circulation may be: (a) in the liver itself (cirrhosis, tumor); (b) prehepatic (portal or splenic thrombosis, tumors or inflammations of the pancreas, enlarged mesenteric lymph nodes); or (c) posthepatic (severe cardiac decompensation with right heart stasis).

In cirrhosis, the large ramifications of the portal vein are well filled, but not the smaller ones. In the next stage, because of stasis, the splenic vein becomes tortuous and collateral circulation then develops through the dilated (varicose) esophageal veins. In cases of tumors, vessels may be displaced by extrinsic masses or, as in the case of retothel-sarcoma of the spleen, newly formed (increased) vascular supply to the tumor may become visible.—*E. R. N. Grigg, M. D.*

Marcozzi, G., Messinetti, S., Colombati, M., and Mocavero, G. La visualizzazione del sistema azigos mediante flebografia vertebrale transomatica. (The visualization of the azygos system using trans-somatic vertebral phlebography.) *Ann. ital. di chir.*, Apr., 1960, *37*, 265–283. (From: Istituto di Clinica Chirurgica Generale e Terapia Chirurgica della Università, Perugia, Italy.)

The authors, after reviewing methods for visualizing the azygos vein by mediastinal laminagraphy and by intraosseous, costal-intraosseous and intraspinous venographic techniques, describe a personal technique that they name "trans-somatic vertebral phlebography."

The patient is placed on the fluoroscopic table in the prone position. A radiopaque landmark is placed on the spinous process of the first or second lumbar vertebra. A special needle designed by the authors (not described or illustrated in the text) is then inserted below the left twelfth rib on the external margin of the longissimus dorsi muscle. The needle, under fluoroscopic control, is directed dorsoventrally and to the right toward the midpoint of the left body surface of L2. In order to reach the body of L1, the needle has to be directed cephalad also.

The puncture of L1 is preferable for elective visualization of the entire azygos vein. The puncture of L2 is recommended for also visualizing the spinal and intercostal veins, which are tributaries of the azygos vein.

Before puncturing the vertebral body, the exact position of the needle tip is determined by a lateral roentgenogram taken with the patient in the prone position. The needle is then pushed by gentle screwing movements into the spongy center of the vertebral body from which blood can be easily aspirated and replaced by slight movements of the syringe plunger. The position of the needle is checked again by posteroanterior and lateral roentgenograms.

At this point, 40 or 50 cc. of angiombrine (Dagra)—which contains 74 per cent iodine and is very fluid—is injected in five or six seconds by a common syringe which is connected to the needle by a polyethylene tube. The best visualization of the azygos vein occurs immediately after the end of the injection. Ten seconds later the left heart cavities are filled and at the eleventh second the thoracic aortogram can be made.

The inferior vena cava also is opacified because the medium refluxes into the vertebral and lumbar veins which are below the injected vertebra and from there passes into the inferior vena cava.

The authors applied this technique in studying mediastinal tumors, superior caval obstruction and portal hypertension syndromes.—*Frank L. Campeti, M. D.*

Di Matteo, G., and Morabito, A. Rilievi anatomo-funzionali sul circolo linfatico nell' arto superiore mediante linfangioadenografia; considerazioni sui fondamenti etiopatogenetici dell'edema indurativo postmastectomia. (Anatomicophysiologic study of the lymphatic system of the superior extremity using lymphangioadenography; consideration of the fundamental etiopathology of postmastectomy indurative edema.) *Ann. ital. di chir.*, May, 1960, *37*, 363–383. (From: Istituto di Clinica Chirurgica dell'Università, Perugia, Italy.)

The authors, after two years of experience with lymphoadenoangiography of the superior extremity, present interesting observations on the morphology and function of the lymphatic system of this area.

The unsettled problem of the hard edema which sometimes follows mastectomy associated with the removal of the axillary lymph nodes is extensively discussed.—*Frank L. Campeti, M. D.*

Di Matteo, G., and Morabito, A. Ricerche sull'anatomia funzionale radiologica del sistema linfatico soprafasciale degli arti in corso di flebopatie infiammatorie e dinamiche. (Radiologic study of the anatomy and function of the suprafascial lymphatic system of the extremities in the course of inflammatory and dynamic phlebopathies.) *Ann. ital. di chir.*, Apr., 1960, *37*, 284–294. (From: Istituto di Clinica Chirurgica dell'Università, Perugia, Italy.)

The authors studied the lymphatic system of the lower extremities in 30 patients affected by thrombophlebitis, venous thrombosis and venous varices. They used the lymphangioadenographic technique according to J. B. Kinmoth *et al.* (*Brit. M. J.*, 1955, *2*, 940) and demonstrated in the majority of their

cases that morphologic and functional alterations of the lymphatic system are concomitant with the venopathies and their functional sequelae. These abnormalities of the lymphatic system are, according to the authors, an important etiologic factor in syndromes of vascular insufficiency, generally considered to be due to primary venous lesions.—*Frank L. Campeti, M. D.*

LIPPMANN, HEINZ I., and GOLDIN, RALPH R. Subcutaneous ossification of the legs in chronic venous insufficiency. *Radiology*, Feb., 1960, *74*, 279–288. (Address: H. I. Lippmann, 1710 Newport Ave., New York 61, N. Y.)

The authors report a series of 60 cases in which subcutaneous ossification of the legs was present. In all of these patients this ossification occurred as a late complication of chronic venous insufficiency with the typical clinical manifestations of a chronic dermatitis and cellulitis, and atrophy of the skin and subcutaneous tissue with induration and brown discoloration being present. The condition was unilateral in 33 and bilateral in 27, giving a total of 87 legs which were evaluated in this study. All patients were females past the menopause, and 57 (95 per cent) had obesity.

The ossification was clearly established to be located in the subcutaneous tissues by means of roentgenograms using soft tissue techniques, venography and, in some instances, laminagraphic studies. In 6 cases there was pathologic confirmation from biopsy specimens obtained during surgical treatment for some complication. The roentgenographic appearance of the ossifications varied according to the amount and extent of involvement. Some showed fine granular densities. Others showed delicate oval or cylindrical densities which often interlaced and coalesced. Frequently these densities demonstrated thin rims and lucent centers which sometimes had a fine web-like pattern. Heavy cords and sheets which retained central lucent zones and trabeculation were also demonstrated in several instances.

The differential diagnosis includes: phleboliths, arterial calcifications, myositis ossificans, calcification of infestations, periarticular ossification associated with disease of the spinal cord, various forms of calcinosis, calcification within localized areas of trauma and necrosis, and Ehlers-Danlos syndrome. Careful evaluation of the calcific densities correlated with the clinical picture will in most cases lead to the proper diagnosis.

Pathologically, the heterotropic tissue consisted of cancellous bone in plates or rings, in the center of which were fat cells. No cartilaginous tissue was encountered and no ossification was found within the lumen or wall of the vein. The pathogenesis of this subcutaneous ossification is being studied but as yet no disturbance in systemic calcium and phosphorus metabolism has been found.—*Donald N. Dysart, M.D.*

RADIATION THERAPY

FRICK, HENRY CLAY, II, TAYLOR, HOWARD C., JR., GUTTMANN, RUTH J., JACOX, HAROLD W., and MCKELWAY, WILLIAM P. A study of complications in the surgical and radiation therapy of cancer of the cervix. *Surg., Gynec. & Obst.*, Oct., 1960, *111*, 493–506. (From: Departments of Obstetrics, Gynecology, and Radiology of the College of Physicians and Surgeons, Columbia University; the Obstetrical, Gynecological and Radiological Service of the Presbyterian Hospital; and the Gynecological and Radiological Service of the Francis Delafield Hospital of Columbia-Presbyterian Medical Center, New York.)

The authors review the complications arising from surgical and radiation therapy for cancer of the cervix in 748 patients who were treated at the Presbyterian and Francis Delafield Hospitals during the years of 1944 to 1957. Because of certain changes which were made in the management of cervical cancer in these hospitals in late 1951 and early 1952, the series is reported in two periods, 1944 to 1951 and 1952 to 1957.

These patients were treated by the following methods: (1) external roentgen rays alone, 82 patients; (2) intracavitary radium and external roentgen rays, 272 patients; (3) radium needles and external roentgen rays, 119 patients; (4) intracavitary radium, external roentgen rays and lymph node dissection, 56 patients; (5) radical operations, 92 patients; (6) radical operations and external roentgen rays, 115 patients; and (7) other, 12 patients. The injuries produced by these methods of therapy were considered in three categories, namely, radiation injuries, surgical injuries and those due to a combination of both.

In reviewing these 748 cases, it appeared that there had been a greater number of fatalities and severe complications in recent years. In the irradiation series two main factors seem responsible: (1) the introduction of the pelvic lymph node dissection after full radiation therapy and (2) the increase in dosage of roentgen therapy. The recognition of these factors resulted in certain changes in the routine of management.

In the patients in whom extensive operation and increased irradiation were combined, these factors were, of course, additive. Preoperative irradiation made the normal tissue less tolerant to operation, and surgical treatment appeared to render tissue more vulnerable to large doses of subsequent irradiation. As a result of the authors' experience with operations performed after roentgen therapy, postirradiation

lymph node dissection has been abandoned in both hospitals.

It has become obvious that treatment with more than 4,000 r in addition to radium, as used with their technique, is hazardous; external irradiation in Stage I and Stage II disease has been reduced to a maximum of 4,000 r tumor dose in four to six weeks with lead shielding in the center of the fields.

An increase in surgical complications in recent years was less apparent; nevertheless, in the earlier period, from 1944 to 1951, there were 12 per cent major complications with no operative mortality and in the latter period 17 per cent major complications and 3 operative deaths. It seemed noteworthy that all of the deaths occurred in patients in whom age or some other constitutional factor had increased the risk. It is the authors' intent to return to a more careful exclusion of the bad risk cases from surgical therapy.—*Ralph M. Scott, M.D.*

Lede, Roberto Enrique. Tratamiento androgenico del carcinoma de mama y embarazo o lactancia, inoperables, agudos, metastasis y recidivas. (Treatment with androgen of acute, inoperable mammary carcinoma associated with pregnancy or lactation, and of metastasis and relapses.) *Prensa méd. argent.*, Mar. 25, 1960, *47*, 764–771. (Address: Rivadavia 4980, Buenos Aires, Argentina.)

In carcinoma of the breast in the first stage (Steinthal's classification), with or without pregnancy, radical mastectomy is recommended, to be followed by roentgen therapy. In the second stage, however, should pregnancy be present, abortion is first performed. In the third stage the pregnancy is also interrupted but, instead of surgery, the patient is subjected to intensive androgen treatment beginning with 100 mg. doses twice daily for five days, then 100 mg. daily for twenty days, then 250 mg. every ten or fifteen days, while roentgen therapy is given. A similar regimen also is advised for cases with "inflammatory" carcinoma, with carcinoma found during the postpartum period, and with metastases or relapses.

In the past four years, the author has seen 56 patients with carcinoma of the breast. When first examined, 24 were Stage I; 20, Stage II; and 12, Stage III. Metastases subsequently were found in 6 of the Stage I group, in 6 of the Stage II group, and in 8 of the Stage III group; relapses occurred in 2 Stage II and 3 Stage III patients.

Treatment with androgen, which has its measure of inconvenience to the patient (virilization), must be carried out to large total doses (up to 8,000 mg.) before it will be really effective. In some cases, though, it permits lengthy, symptom-free survival and consequently deserves to be given a trial when other palliative methods have been unsuccessful.—*E. R. N. Grigg, M.D.*

Uhlmann, Erich M., and Ovadia, Jacques. High-energy electrons in the treatment of malignant tumors of the thorax. *Radiology*, Feb., 1960, *74*, 265–272. (Address: E. M. Uhlmann, Tumor Clinic, Michael Reese Hospital, Chicago 16, Ill.)

Of the malignant neoplasms within the thoracic cage the primary carcinomas of the esophagus and of the bronchus continue to present the highest death rates. Although the absolute number of individuals who have been successfully treated has increased, the five year survival percentage figures have shown little improvement. One of the main problems of radiation therapy has been that the tumor dose of ionizing radiation necessary for control of these neoplasms is so large that it often cannot be tolerated by the afflicted patients. Now, through the modality of high energy electrons, large doses of effective ionizing radiation can be applied to deep-seated tumors with a relatively low integral dose to healthy tissue and consequent good tolerance by the patient.

In the treatment of carcinoma of the esophagus, narrow anterior and posterior fields of varying lengths up to 20 cm. were utilized, and appropriate lucite wedge filters were employed when necessary to produce a more uniform dose. The energy used depended on the anteroposterior diameter of the thoracic cage and was usually in excess of 30 mev. The dose to the spinal column was kept below 4,500 r. Of the 16 patients with carcinoma of the esophagus so treated, 10 received a minimum of 6,000 r to the esophagus, which was considered a satisfactory therapeutic dose. Of the 10 patients who received a full course of therapy, 4 subsequently died, 2 from unrelated causes after two years and one-half year. The 6 living patients have survived for varying periods up to nineteen months. There were no serious complications attributable to the radiation therapy. In the treatment of bronchogenic carcinomas, lucite wedges were also used when necessary to achieve a more uniform dose. Of the 22 patients treated for carcinoma of the bronchus, 17 received a full course of therapy. Of these 17 patients 4 died, with unrelated causes responsible for the death of 2. Of the 13 surviving, 2 have remained free of symptoms for one year, 5 for more than six months, and 6 for less than six months.

The preliminary therapeutic results must be interpreted with the knowledge that none of these patients was operable and that most of them were of advanced age and debilitated by their disease. It is felt that objective evaluation demonstrates the effectiveness of therapy with high energy electrons in these advanced cancers. From experience with electron therapy in other areas of tumors which were less advanced and offered a better prognosis, it is believed that the utilization of high energy electrons in the treatment of earlier diagnosed carcinomas of the esophagus and the bronchus is justified and should

result in a considerably higher five year survival rate than can be achieved at present with conventional methods of radiation therapy and surgery.—*Walter H. Jarvis, Jr., M.D.*

Woodley, R. G., Bronstein, E. L., and Laughlin, J. S. Exit dosimeter for effective patient thickness. *Radiology*, Feb., 1960, *74*, 273–278. (Address: R. G. Woodley, 444 E. 68th St., New York 21, N. Y.)

An adequate radiation treatment plan should give the actual dose distribution at important points within the patient. Usually the treated area is not of homogeneous density and a correction must be applied. One practical and versatile method of making corrections is by an exit dosimeter, where the exit dose from the body or part is measured relative to the maximum dose.

The authors present the design, construction and calibration of such an instrument which consists of a parallel plate ionization chamber with dag-coated polystyrene walls. Exit dose measurements were made in 24 patients and the results are presented in tabular form.

In general, the exit dose measurements are most valuable when the fields are in the region of air-containing lung. An example is given in which a conventional treatment plan would have underestimated the actual tissue dose by 25 per cent.—*Edward B. Best, M.D.*

RADIOISOTOPES

Werner, S. C., Row, V. V., and Radichevich, I. Nontoxic nodular goiter with formation and release of a compound with the chromatographic mobility characteristics of triiodothyronine. *J. Clin. Endocrinol. & Metabol.*, Oct., 1960, *20*, 1373–1383. (From: Department of Medicine and Biochemistry, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital in New York, New York.)

Isolated instances have been reported in which l-triiodothyronine has been identified as the major I^{131} labeled iodinated compound in the serum by paper chromatography. The authors report an additional case, that of a fourteen year old girl with a nontoxic goiter of two years' duration.

The history was negative except for a small goiter which had appeared two years before and had enlarged slowly. Administration of l-thyroxine and l-triiodothyronine had apparently arrested the further growth of the goiter. On physical examination the left lobe and isthmus seemed enlarged and the isthmus was cystic to palpation. A bruit was audible in the right supraclavicular area. Initially, while the patient was taking thyroxine, the twenty-four hour I^{131} uptake was 2 per cent and the serum protein iodine was 2.4 μgm. per 100 ml.; butanol-extractable iodine (BEI) was 1.6 μgm. per 100 ml. Three weeks after discontinuation of oral T_4 therapy, twenty-four hour thyroidal I^{131} uptake was 22 per cent and a scan showed the activity to be spread diffusely over a right lobe of normal size and over the superior pole of the enlarged left lobe.

Thyroidectomy was performed and the enlarged left lobe was removed. A pathologic diagnosis of nontoxic nodular goiter was returned. Three months postoperatively the patient was euthyroid and the serum protein bound iodine level was 4.0 μgm. per 100 ml.

Chromatographically, approximately 90 per cent of tracer I^{131} activity in venous and arterial blood was present in the iodothyronine fraction, with the T_3 area exceeding that of the T_4 area in all samples, although T_4 accounted for about 30 to 40 per cent of the total distribution. The nodular gland tissue, on the other hand, exhibited almost all of its radioactivity in the T_3 area, with no T_4. Of the remaining radioactivity 15 per cent was present as MIT and DIT, constituting a reversal of the normal thyronine:thyrosine ratio, which is of the order of 1:8 in the euthyroid gland. In two dimensional chromatograms of the digested nodular tissue the compound termed by the authors T_3 migrated as did the stable 1-3-5-3′-T_3 which was used as a standard. Its migration was separate from all other compounds.

Preoperatively, and when receiving no medication, the patient had a protein bound iodine level of 4.7 μgm. per 100 ml., of which approximately 2.3 μgm. per 100 ml. was present as T_3. Since l-triiodothyronine has been estimated in man to have roughly 45 times the activity of T_4, the authors estimate that a thyroxine level equivalent to 9 to 11 μgm. per 100 ml. might have been present. Since the patient was not hyperthyroid and the thyroid was not turning over radioiodine unduly rapidly, it was suspected that the compound identified chromatographically as T_3 might not be the naturally occurring form, 1-3-5-3′, but an analogue, such as the d-form, the reverse form (1-3-3′-5′), diiodothyronine (T_2) or a conjugate. It is suggested that these compounds could not be distinguished from l-T_3 by the usual chromatographic procedures.

Further chromatographic analysis served to eliminate all of these possibilities except the d-form of T_3, a phenomenon not heretofore described in humans. No definite explanation for the d-form of T_3 can be arrived at except for the possibility that there was a localized derangement of thyroid function which resulted in the production of d-amino acids.—*Frederick J. Bonte, M.D.*

Adams, R., Specht, N., and Woodward, I. Labeling of erythrocytes *in vitro* with radioiodine-tagged l-triiodothyronine as an index of thyroid function: an improved hematocrit correction. *J. Clin. Endocrinol. & Metabol.*, Oct., 1960, *20*, 1366–1372. (From: Depart-

ments of Radiology and Internal Medicine, College of Medical Evangelists, Los Angeles, California.)

As a test of thyroid function the *in vitro* labeling of erythrocytes with I^{131} tagged l-triiodothyronine is gaining widespread attention. Because it can be used as a radioiodine test in children and young adults and in pregnant females without the necessity of administering the tracer isotope to the patient, this test is now being examined critically in many laboratories. Recently, a number of suggestions for improvement in technique and calculation have been made including the one by the present authors. They point out that the quantity of radioiodinated T_3 is proportional to the product of the reactants, conforming to the law of mass action, with the reactants being the red blood cell mass and the concentration of labeled T_3 in the surrounding plasma.

The authors adduce evidence to show that labeled T_3 taken up by the red blood cells appears to be approximately proportional to the product of the red blood cell mass and the concentration of I^{131} l-triiodothyronine remaining in the plasma at the end of incubation. It is further pointed out that, in the original method of Hamolsky, correction is made for variation with the hematocrit of the red blood cell mass but not for the level of l-triiodothyronine concentration as influenced by the hematocrit and the transfer of labeled T_3 from the plasma to the cells during labeling. It has been shown that the red blood cell uptake as calculated by Hamolsky's method might appear to be in the hypothyroid range because of a low hematocrit, or in the hyperthyroid range in cases of polycythemia. The authors point out that inconsistent results obtained by investigators other than the original team resulted in samples with high or low hematocrits.

Accordingly, the authors propose calculation of results by a method independent of the hematocrit over any reasonable clinical range. The following equation is used to calculate the binding coefficient, *K:*

$$K = \frac{X/A(1-H)}{H(1-X/A)}$$

where X is the quantity of labeled T_3 bound by the cells during incubation, A is the total labeled l-triiodothyronine added to the blood sample, and H is the hematocrit.

From their experience thus far, the authors suggest the following ranges for K: euthyroid, 0.10–0.18; hypothyroid, 0.06–0.10; and hyperthyroid, 0.18–0.35.

It is further suggested that for reproducible results, all details of labeling and washing should be standardized within a laboratory and that the fewest washings should be employed consistent with adequate removal of plasma, with about three washes appearing to be the optimal procedure.

It is concluded that, because of its relative independence of the hematocrit, the binding coefficient, K, is a more reliable index of thyroid function than is the percentage red blood cell uptake per 100 hematocrit commonly employed in this test. The suggestion embodied in this paper is well worth considering.—*Frederick J. Bonte, M.D.*

Crane, C. W., and Neuberger, A. Absorption and elimination of ^{15}N after administration of isotopically labelled yeast protein and yeast protein hydrolysate to adult patients with coeliac disease; I. Rate of absorption of ^{15}N yeast protein and yeast protein hydrolysate. *Brit. M. J.*, Sept., 1960, *2*, 815–823. (Address: C. W. Crane, Department of Medicine, Queen Elizabeth Hospital, Birmingham 15, England.)

This article records the findings of the rates of absorption after feeding whole yeast protein and hydrolysate labeled with the stable iostope N^{15}. The authors have presumed that metabolism proceeds along the same pathways and at the same rate as in normal subjects once the nitrogen is absorbed into the body.

Four patients suffering from adult celiac disease were studied with one normal adult as a control. The yeast protein and yeast protein hydrolysate labeled with the stable isotope were administered to the patient and urine was collected at half hour intervals. The isotope content of the ammonia and urea in the urine and, in a few experiments, that of the urea and amino acids of the venous plasma was measured.

The appearance of the isotope in the various fractions mentioned was considerably delayed as compared to normal subjects. In the case of the whole protein, the maximum amount of the isotope was present two to two and one-half hours after the ingestion of the labeled material, whereas in the normal subjects the maximum was observed at about fifty minutes. With the protein hydrolysate, deviations from normal were more valuable than with the whole protein and, on the whole, were less marked.

The various factors repsonsible for this delay in absorption are considered. The possibility that hypomotility of the small intestine may be partially responsible has not been excluded. The authors conclude however, that the rate of absorption of peptids and amino acids is reduced in adult celiac disease by a reduction in the effective absorptive surfaces.—*Ralph M. Scott, M.D.*

Stevenson, J. J. Localization of radio-active implants with image intensification and television. *Proc. Roy. Soc. Med.*, Aug., 1960, *53*, 642–645. (From: Royal Marsden Hospital and the Institute of Urology, London, England.)

The author describes the modifications of the

equipment used for the localization of radioactive implants of the pituitary gland at his institution over the last five years, during which time more than 200 patients were so treated.

Initially the localization of the introducing needle and the subsequent implantation were done by means of fluoroscopy in two planes. Because of the disadvantages inherent in this method, image intensification began to be used. Here the detail was satisfactory but surgeons had difficulty in adapting themselves to the use of the viewing attachments.

The problem was solved by the use of an industrial television chain in conjunction with the image amplifier. The camera is smaller and lighter than the reflecting viewer which it replaces. Detail on the television screen in the frontal and sagittal planes is described as being adequate, but not quite as good as with the optical device. The current in the roentgen-ray tube has to be approximately double. Inasmuch as the monitor is placed some distance away from the patient, there is no significant increase in dose to the observers.

The author states that he has found no major disadvantages in its use and the operating time has been speeded up considerably.—*Ralph M. Scott, M.D.*

MISCELLANEOUS

Hodara, Morris, Friedman, Milton and Hine, Gerald J. Radiation dosimetry with fluorods (miniature glass rod dosimetry). *Radiology*, Nov., 1959, *73*, 693–706. (Address: M. Hodara, Radiation Therapy Department, Hospital for Joint Diseases, New York 35, N. Y.)

The authors discuss a method of dosimetry utilizing a miniature radiation-sensitive glass rod. This 1 mm.×6 mm. glass rod consists of silver-activated phosphate glass. Following irradiation, some of the silver ions are converted to silver atoms by capturing electrons ejected from the glass by the ionizing radiation. The rods are then irradiated by ultraviolet light, which produces an orange fluorescence from the silver atoms. The number of silver ions converted into atoms can therefore be used as a measure of dose when the fluorod is placed in an ultraviolet fluorimeter, the design of which is described in some detail.

The small dimensions and chemical inertness of the fluorod make it an ideal dosimeter. Some of the characteristic properties of the fluorod dosimeter that have been noted include linearity of response with dose, temperature independence, directionality independence, and a slow fading of fluorescence. Heat treatment for approximately five hours at 400° C. will reduce the dose effect to background level so that the fluorod may be used again. Due to energy dependence, fluorods should be used only for energies higher than 400 kv. peak roentgen rays. Fluorods should not be used with very large fields. When the field size is increased beyond 150 sq. cm., the contribution of scattered radiation increases the readings more rapidly due to enhanced sensitivity of the fluorods to the lower energy scattered radiations.

The dosimetric properties of the fluorod were found to be ideal for *in vivo* dosimeters. When fluorod measurements were compared with ionization chamber measurements of central axis depth dose, entrance and exit dose, tangential beam dose, and rotational therapy, good agreement was found between the two methods. The potential usefulness of the miniature fluorod in clinical radiation therapy at the supervoltage level appears unlimited.—*John S. Alexander, M.D.*

Troup, J. B., and Bickel, W. H. Malignant disease of the extremities treated by exarticulation; analysis of two hundred and sixty-four consecutive cases with survival rates. *J. Bone & Joint Surg.*, Sept., 1960, *42-A*, 1041–1050. (From: Section of Othopaedic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

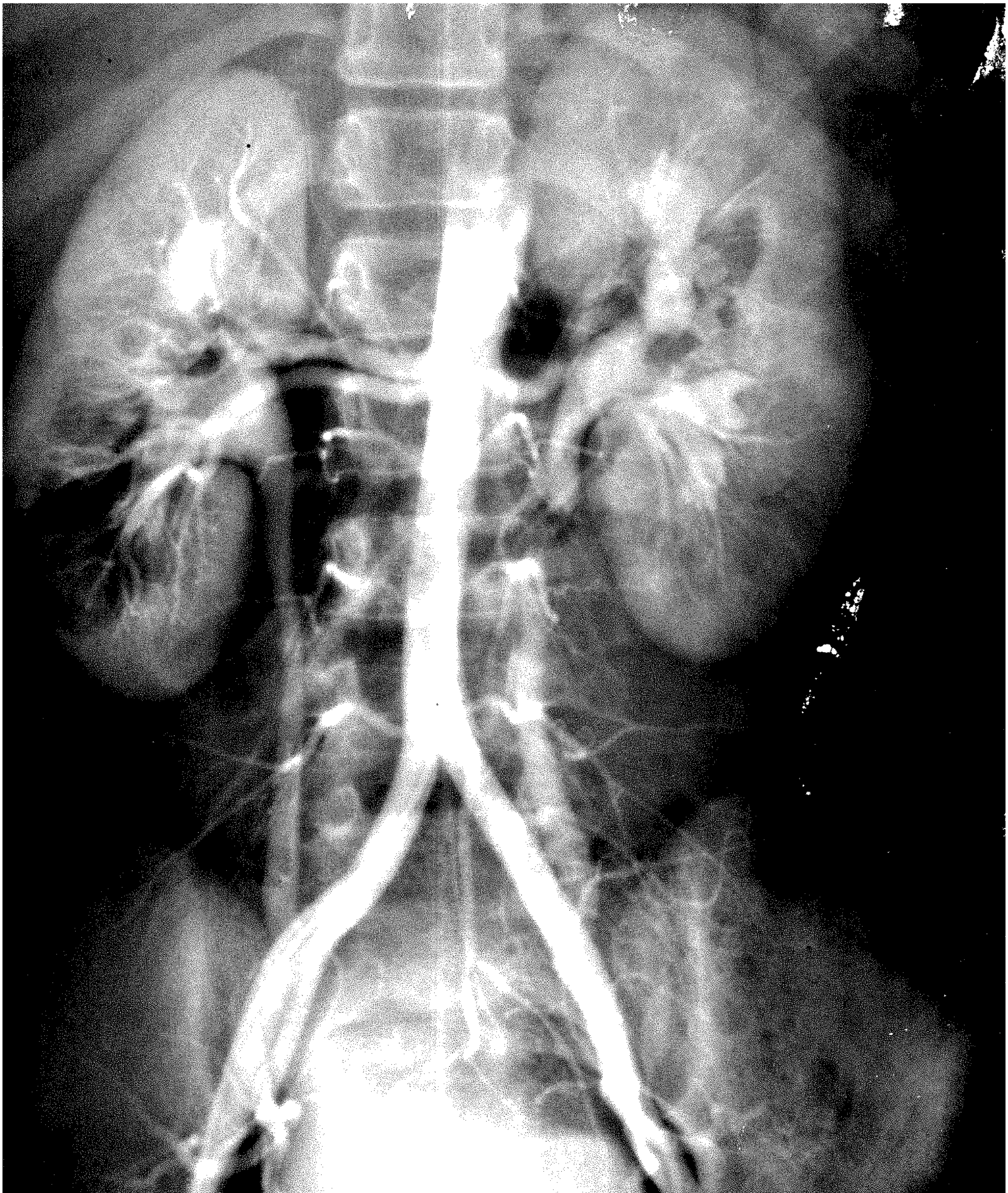
The survival rates in 264 cases of exarticulation for malignant disease are summarized; there was only 1 hospital death.

Five years after surgery, 41.5 per cent of traced patients with hindquarter amputation and 39.6 per cent of traced patients with hip joint disarticulation were living. In some cases amputation was done to relieve intractable pain or a fungating lesion.

Five years after surgery 40.6 per cent of traced patients with forequarter amputation and 19.2 per cent of 25 traced patients with shoulder joint disarticulation were living. Forequarter amputation has superseded shoulder joint disarticulation in soft tissue tumors of the upper extremity.

The common course of soft tissue fibrosarcoma and liposarcoma was successive recurrences at the amputation site with eventual metastases. Fibromyosarcoma has the best prognosis of the soft tissue tumors with 6 of 10 traced patients surviving five years. Chondrosarcoma gave the best prognosis of the bone tumors, while that of osteogenic sarcoma was poor. Eleven of 68 traced patients with osteogenic sarcoma survived more than five years; 21 of 53 traced patients with chondrosarcoma survived more than five years.

Early radical operation gave gratifying results but hindquarter amputation had a poorer prognosis when it followed unsuccessful attempted local resection of bone tumor than when it was done as a primary procedure. The prognosis also was poor when symptoms were present more than three months, when there was surgical intervention without immediate definitive treatment, in cases of extensive local progression and tumors of borderline operability.—*Martha Mottram, M.D.*



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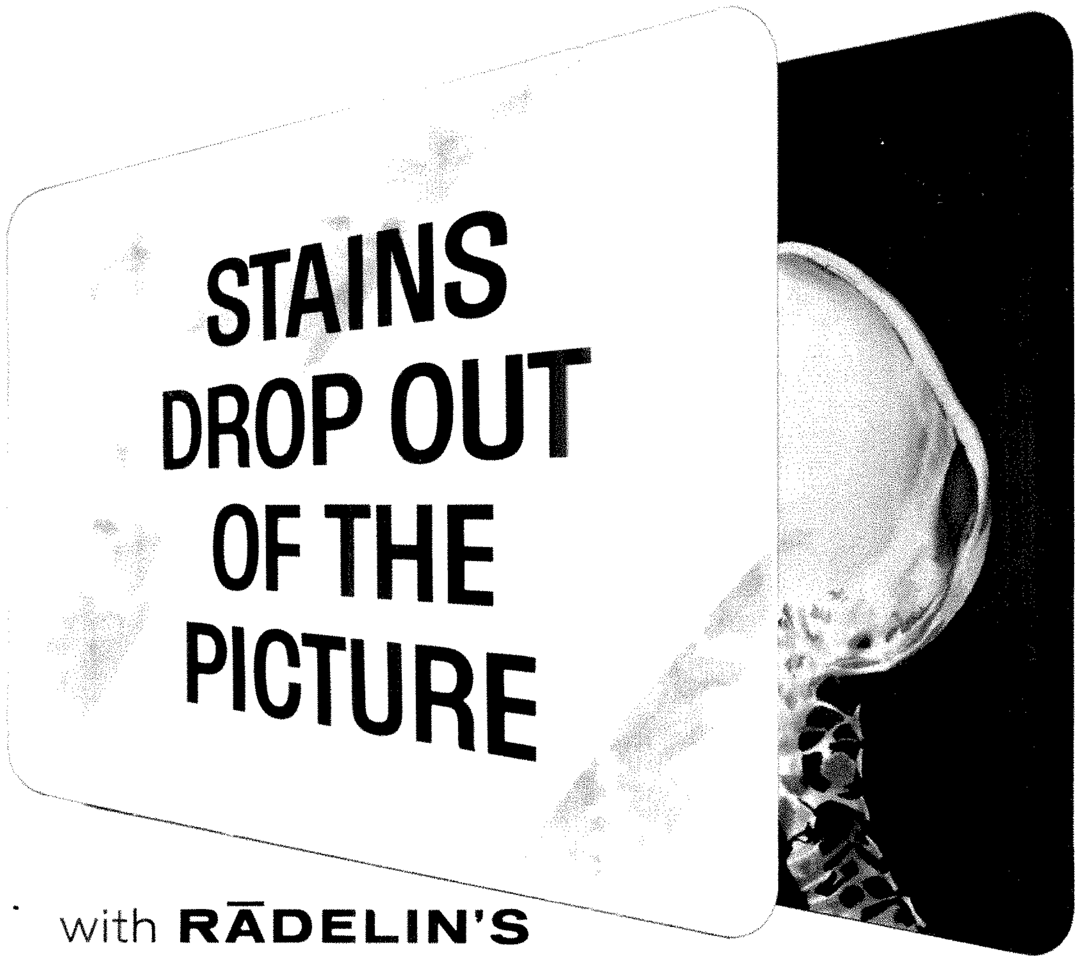

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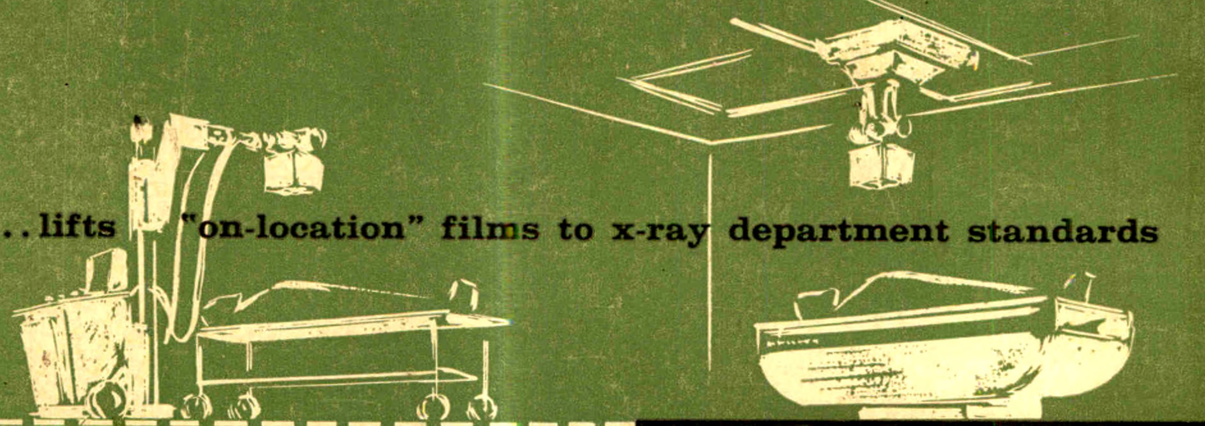

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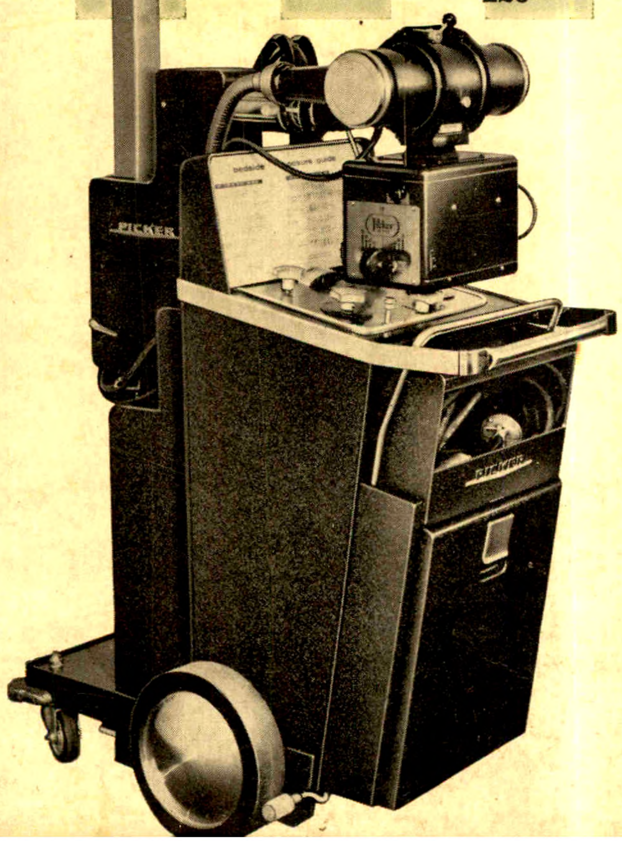

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